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[1]*No. 1, 1902, Biological Laboratory.*—Preliminary Report of the Appearance in the Philippine Islands of a Disease Clinically Resembling Glanders. By R. P. Strong, M. D.

No. 2, 1902, Chemical Laboratory.—The Preparation of Benzoyl-Acetyl Peroxide and Its Use as an Intestinal Antiseptic in Cholera and Dysentery. Preliminary Notes. By Paul C. Freer, M. D., Ph. D.

[1]*No. 3, 1903, Biological Laboratory.*—A Preliminary Report on Trypanosomiasis of Horses in the Philippine Islands. By W. E. Musgrave, M. D., and Norman E. Williamson.

[1]*No. 4, 1903, Serum Laboratory.*—Preliminary Report on the Study of Rinderpest of Cattle and Carabaos in the Philippine Islands. By James W. Jobling, M. D.

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[1]*No. 11, 1903, Biological Laboratory.*—Entomological Division, Bulletin No. 1: Preliminary Bulletin on Insects of the Cacao. (Prepared Especially for the Benefit of Farmers.) By Charles S. Banks, Entomologist.

[1]*No. 12, 1903, Biological Laboratory.*—Report on Some Pulmonary Lesions Produced by the Bacillus of Hæmorrhagic Septicæmia of Carabaos. By Paul G. Woolley, M. D.

No. 13, 1904, Biological Laboratory.—A Fatal Infection by a Hitherto Undescribed Chromogenic Bacterium: Bacillus Aureus Fœtidus. By Maximilian Herzog, M. D.

[1]*No. 14, 1904.*—*Serum Laboratory:* Texas Fever in the Philippine Islands and the Far East. By J. W. Jobling, M. D., and Paul G. Woolley, M. D. *Biological Laboratory:* Entomological Division, Bulletin No. 2: The Australian Tick (Boophilus Australis Fuller) in the Philippine Islands. By Charles S. Banks, Entomologist.

No. 15, 1904, Biological and Serum Laboratories.—Report on Bacillus Violaceus Manilæ: A Pathogenic Micro-Organism. By Paul G. Woolley, M. D.

[1]*No. 16, 1904, Biological Laboratory.*—Protective Inoculation Against Asiatic Cholera: An Experimental Study. By Richard P. Strong, M. D.

No. 17, 1904.—New or Noteworthy Philippine Plants, II. By Elmer D. Merrill, Botanist.

[1]*No. 18, 1904, Biological Laboratory.*—I. Amebas: Their Cultivation and Etiologic Significance. By W. E. Musgrave, M. D., and Moses T. Clegg. II. The Treatment of Intestinal Amœbiasis (Amœbic Dysentery) in the Tropics. By W. E. Musgrave, M. D.

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[1]*No. 23, 1904, Biological Laboratory.*—Plague: Bacteriology, Morbid Anatomy, and Histopathology (Including a Consideration of Insects as Plague Carriers). By Maximilian Herzog, M. D.

No. 24, 1904, Biological Laboratory.—Glanders: Its Diagnosis and Prevention (Together with a Report on Two Cases of Human Glanders Occurring in Manila and Some Notes on the Bacteriology and Polymorphism of Bacterium Mallei). By William B. Wherry, M. D.

No. 25, 1904.[2]—Birds from the Islands of Romblon, Sibuyan, and Cresta de Gallo. By Richard C. McGregor.

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No. 30, 1905, Chemical Laboratory.—I. Autocalytic Decomposition of Silver Oxide. II. Hydration in Solution. By Gilbert N. Lewis, Ph. D.

No. 31, 1905, Biological Laboratory.—I. Notes on a Case of Hæmatochyluria (Together with Some Observations on the Morphology of the Embryo Nematode, Filaria Nocturna). By William B. Wherry, M. D., and John R. McDill, M. D., Manila, P. I. II. A Search Into the Nitrate and Nitrite Content of Witte's "Peptone," with Special Reference to Its Influence on the Demonstration of the Indol and Cholera-Red Reactions. By William B. Wherry, M. D.

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[1] Out of print.

[2] The first four bulletins in the ornithological series were published by the Ethnological Survey under the title "Bulletins of the Philippine Museum." Later ornithological publications of the Government appeared as publications of the Bureau of Government Laboratories.

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B. MEDICAL SCIENCES

VOL. III DECEMBER, 1908. No. 6

STREPTOTHRICOSIS WITH SPECIAL REFERENCE TO THE ETIOLOGY AND CLASSIFICATION OF MYCETOMA.[1]

By W. E. MUSGRAVE and M. T. CLEGG, with
a bibliography by MARY POLK.

(From the Biological Laboratory and the Library, Bureau of Science, Manila, P. I.

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[1] To be read in abstract at the Bombay Medical Congress, February 23, 1909.

INTRODUCTION.

Before entering on a study of the etiology of mycetoma, it is necessary to define the disease. This is exceedingly difficult, either from a clinical or an etiologic standpoint.

Formerly the diagnosis was based upon a clinical picture the essentials of which were a chronically enlarged foot with sinusses from which were discharged small granules of various colors and consistency, accompanied by a peculiar, oily degeneration of the tissues. Further classification was made principally upon the color of the granules; black, ochroid, white, red and mixed varieties being recognized. However, when bacteriologic studies began to show the multiplicity of the organisms concerned in the production of Madura foot it became necessary either to consider it a clinical entity of multiple etiology or to attempt an etiologic classification. This was made still more imperative by the discovery that the organisms causing this symptom complex were found also producing lesions in other parts of the body. A number of authors have continued to use a clinical classification, while others have attempted to give one based upon etiologic findings. The result is great confusion in the nomenclature of the disease.

As a prerequisite to an etiologic classification and definition of mycetoma it is necessary first to know and to be able to classify the etiologic factors concerned. So far this has not been done satisfactorily. The botanists are hopelessly confused in their grouping of the organisms and in consequence medical men have been unable properly to identify them. In the first place, authorities differ as to where the group of organisms belongs in the vegetable kingdom, some placing it among the bacteria and others higher up among the fungi. Practically all the latest writers upon the subject agree as to the great similarity between the various species of these organisms and the majority have placed them as species of a single genus, or as parts of two or even three closely allied genera. In order to establish a uniform and clear conception, and after carefully studying all phases of the question we have decided tentatively to accept *Streptothrix* Cohn 1875 as the generic name of the group of organisms under discussion.

The result of this decision is that the other names given to the tentative genus, such as *Actinomyces, Nocardia, Oöspora,* etc., become synonyms, the disease streptothricosis being limited to infection with parasites properly belonging to the genus, the various species of which will be considered presently.

Adopting such an interpretation, we have a fairly definite group of organisms with reasonably uniform pathologic and clinical manifestations, connected with other groups of closely related organisms giving somewhat similar manifestations. For example, the *Oïdia* or *Blastomyces* on the one hand and the tubercle bacilli on the other, may somewhat closely resemble the *Streptothricæ* in their action in certain parts of the body.

Mycetoma may be defined and classified in one of three ways, if *Streptothrix* is accepted as the most available generic name.

(1) It may be considered as a clinical disease of multiple etiology (which may or may not be limited to *Streptothrix* infections; (2) the term may appropriately be made synonymous with streptothricosis, actinomycosis, nocardiosis, etc.; (3) it may be made a clinical type (foot infection) by a *Streptothrix* (*Actinomyces* or *Nocardia*). Each of these classifications has something in its favor and also may be criticised.

The first would make diagnosis easy, for all forms of foot enlargement giving certain clinical manifestations regardless of the etiology, known or unknown, might be included, but it is open to the objection of not being definite and does not conform to our present methods of etiologic classification.

The second method has much in its favor and is practically adopted by Manson. The objections to it are that it adds a new significance to a term which does not clearly express the conditions and also adds a further synonym to a group of infections already rendered confusing by the number of its synonyms. The difficulty can more satisfactorily be met by the third method.

We have therefore decided to follow the third classification making mycetoma a *clinical* type or variety of streptothricosis—*Streptothricosis pedis*—and to define it as follows:

A disease consisting of a *Streptothrix* infection of the foot (*Streptothricosis pedis, Actinomycosis pedis*), characterized by a chronic course, swelling and deformity of the part, a peculiar, oily degeneration of the tissues with cavity and sinus formations and the discharge through the fistulous openings of mycotic aggregations containing the microörganisms.

Mycetoma, with this definition, becomes so intimate a part of streptothricosis that a balanced conception of it can only be obtained by a study of the whole subject of streptothricosis and a classification of the organisms concerned.

For this reason, the scope of this paper has been enlarged to include a discussion in two parts of the whole subject of *Streptothrix* or *Nocarida* infections.

PART I.

ORIGINAL WORK.

MATERIAL.

The material for this paper consists of the following cultures:

1. *S. freeri* Musgrave & Clegg, *This Journal* Sec. B. (1907), **2**, 477.
2. *S. maduræ* Vincent. (This culture was sent to us by Professor Foulerton who writes as follows concerning it: "This culture has been in my hands for the last ten years; it corresponds with Vincent's description of his organism, and

is apparently of the same stock as that from which all the cultures in the London laboratories are derived.")

3. *S. maduræ* Vincent. (This culture was sent to us by Professor Binot of the Pasteur Institute in Paris.)

4. *S. maduræ* Vincent. (This organism was isolated by Dr. R. P. Strong from a case of the pink variety of mycetoma in India, and the culture has been given by him to us, for study.

5. *Streptothrix* of human actinomyces. (From Binot of the Pasteur Institute in Paris.)

6. *Streptothrix* of "*farcin de boeuf*" "A". (From the late Professor Nocard through Binot.)

7. *S. nocardii.* (From Foulerton who writes that "this culture was given to me by Nocard some six years ago.")

8. *S. eppingeri* "A".

9. *S. eppingeri* "B". (Both of these cultures are from Foulerton who writes as follows: "'A' is a descendant of what I believe to have been Eppinger's original culture, 'B' a culture isolated by myself from a case which has not yet been published in detail. I have examined also a third culture of this species obtained by Dr. McDonald from a third case (*The Scottish Medical and Surgical Journal*, 1904). All three strains evidently belong to the same species."

10. *S. capræ* Silberschmidt. (Received from Professor Silberschmidt of Zürich through Binot.)

11. *S. canis* Levy. (From Professor Levy of Strassburg through Binot.)

12. *S. chalcea* Foulerton. (Received from Foulerton who writes that this is a saprophytic species isolated by him from the air.)

The following cultures have also been received, but failed to develop on transplantation:

S. maduræ Vincent. (Furnished by Professor Vincent of the Val du Grace, Paris.)

S. maduræ. (From Legrain de Bougie through Binot.)

Streptothrix of bovine Actinomyces. (From Binot.)

Streptothrix of "*farcin de boeuf*" "N". (From the late Professor Nocard through Binot.)

Streptothrix of Eppinger ("A") and (Kl). (From Binot.)

Streptothrix of Deci. (From Binot who writes regarding this culture that "it was isolated by Deci in the Argentine Republic from a human case resembling tuberculous meningitis." Binot further states in his letter that all the cultures which he has forwarded to us were received by him directly from their authors).

Streptothrix "32". (Received from Foulerton who writes that this organism was isolated by him from a kidney removed from the living patient by operation; the organism was demonstrable in sections of the kidney and was present in large quantity. It is briefly referred to as *S. hominis III* in the *Lancet* (1906), 1, 970. "This organism resembles closely some of the apparently purely saprophytic species, and the infection in the case was probably primary in the lungs."

Streptothrix isolated from a case of mycetoma by Dr. Chaterjee of India.

Dr. Homer Wright states, in reply to a letter regarding cultures of *Actinomyces* and his "*Hyphomycete*," that he no longer has cultures of these organisms.

A comparative study under conditions as nearly alike as possible has been made of all these strains, with due consideration of their morphology, biology, and pathogenic character. All of them, to obviate as much as possible any influence of long cultural environment were, where feasible, first passed through animals and the studies then made from the reclaimed cultures taken from the experimental lesions. All the cultural and other biologic properties have so far as we have been able to do so, been studied under the same conditions in regard to media, temperature, and generation from animal lesions. Our results and consequent descriptions show some variation from previous descriptions of some of these organisms, but in general the picture is very much as given by the original authors.

We have failed entirely to obtain a culture of the Wolf and Israel and Wright type of *Actinomyces,* but, because of the great importance of this organism in the discussion, we have, for comparative purposes, taken James Homer Wright's description of it from his classical monograph. We have also failed to secure a definite culture of Bostroem's *Actinomyces,* although the one sent by Professor Binot from the Pasteur Institute is probably of this species. However, in view of a possible mistake we have used both the description given by Bostroem as well as the Pasteur Institute culture in our comparative work. The important characteristics of our cultures are shown in the following descriptions and are summarized in the attached table.

No. 1. *Streptothrix freeri.* This organism was isolated by us from a case of the ochroid variety of mycetoma and has already been fully described (*This Journal, Sec. B* (1907), 2, 477). It is identical with Eppinger's organism which will be discussed subsequently in this paper, and the name given by us in the first publication should fall as a synonym for *S. eppingeri,* the latter having priority. Other described organisms of the group which are probably identical with this are those of Stokes, Aoyama and Miyamoto, MacCallum, Sabrezes and Rivière, and possibly several others.

No. 2. *Streptothrix maduræ.* This organism has been carefully described by Vincent, Foulerton, and others. A summary of its characteristics are given both in the text and table and in our first report and are again shown in the table attached to this paper. Our work with cultures of this species has been in the main confirmatory of the published results of others. We have worked with three cultures received respectively from Foulerton, Binot, and Strong. These strains are identical in every particular except that the one from Binot is less pathogenic for monkeys than either of the other two.

Morphologically this species gives very constant results. The colonies are made up of intertwining, long filaments which may, or may not, be radially placed at the periphery. There is true branching, but no club formation in cultures and none in experimental lesions in monkeys up to fourteen days. The organism takes the usual aniline stains; it is Gram positive, but is neither acid nor alcohol fast.

Culturally it is a facultative aërobe with strong oxygen requirements. It grows well in the incubator and at tropical room temperature. Positive transplants on artificial media are readily made, but some difficulty is often encountered in securing growth from experimental lesions. This difficulty is greatest when large quantities of the material are transferred to the media, probably because of an inhibiting material in the contents of the lesions. This hypothesis is supported by the fact that development is much more easily secured if the granules from the lesions are washed in sterile salt solution before transferring them to artificial media. Growth on satisfactory media becomes apparent in from two to four days; development gradually continues for several weeks, depending somewhat upon the quantity of medium present. The principal characteristics of growth on various types of media are shown in the table.

Pathogenicity: Several monkeys have been successfully infected with the Foulerton and Strong strains of this organism, but results with the one from the Pasteur Institute were all negative. Intra-abdominal inoculation has proved the most satisfactory and under similar conditions the character of the lesions produced varies but little. The lesions consist of nodular, tubercle-like processes in the omentum, abdominal wall, and contiguous tissues. These lesions break down and become surrounded by pockets and channels containing a peculiar, pus-like material in which may be found the microörganisms. (See also animal experiments.)

No. 3. *Streptothrix maduræ.* (Pasteur Institute culture.) This is identical in all essentials with *S. Vincent* except that it is not pathogenic for monkeys. This may be due in part at least to its long cultivation on artificial media.

No. 4. *Streptothrix maduræ.* (Strong's culture.) This organism is identical with Vincent's species and its description has been included in the above.

No. 5. *Streptothrix actinomyces.* This culture was received from Professor Binot of the Pasteur Institute as human *Actinomyces.* It is quite different from the Wright type and it also appears to have slight distinctions from the Bostroem type of *Actinomyces.*

Morphologically it appears in the tissues as a fungus of the ray type, but without clubs in young experimental lesions. In colonies the cultures are dark, almost black in color, are made up of the branching filaments and transformation products, generally with radial arrangement of the terminals at the margins of the colonies.

The organism stains poorly by the usual laboratory methods; it is Gram positive and neither acid nor alcohol fast.

Culturally it is a facultative aërobe and grows on the majority of the usual media. In reclaiming cultures from experimental lesions this organism acts very much like *S. madurae* mentioned above; however, if the colonies are first washed in distilled water and then transplanted to artificial media, growth takes place without difficulty.

This type, like the majority of the species examined, grows better in media containing sugar or glycerine. Pigment is produced in all media and the body of the medium is generally darkened to a considerable extent by the culture. The pigment varies from an ochre-yellow in ordinary agar to a dark, almost black color in glycerine-agar and on potato.

The characteristics on varous media are shown in the table.

Pathogenicity: This species is pathogenic for monkeys by intraperitoneal inoculation. It produces the usual actinomycotic lesion like those seen in the clinical disease in man and animals. The organisms are found in the broken-down mass discharged from the sinusses.

No. 6. *Streptothrix* of *farcin du boeuf* "A," and

No. 7. *Streptothrix nocardii.* These two strains are identical in all essential particulars and may therefore be described together under the correct name of *S. nocardii.*

Nocard's original description of this organism was not very complete, but several other observers have studied his and other strains and a number of good descriptions have been given. Foulerton has devoted careful study to this species and our work is in general confirmatory of his description. We have already noted the principal characteristics of this organism in both the text and table in our first report and a summary is also shown in the table in this one. Photomicrographic illustrations of its appearance in cultures are also submitted.

Morphologically this parasite shows marked variation under different environment. In young cultures and early lesions the hyphal forms are prevalent and quite uniform in appearance, but in older cultures and in colonies from lesions, irregularities are encountered. Coccus and bacillus-like forms predominate and very old cultures may almost have the appearance of mixed culture of bacteria. The filaments may or may not be radially placed at the periphery of the colonies. There is true branching, but no true clubs have been seen in cultures or in experimental lesions up to fifteen days of age. The Gram-Weigert method of staining gives good results and portions acid fast to the Ziehl-Neelsen-Gabbett method of staining are very numerous. The organism is also alcohol fast.

Culturally this species is a facultative aërobe. It grows on the majority of laboratory media at incubator or tropical room temperature; development becomes apparent in from two to four days after inoculation. The difficulty of securing transplants from experimental lesions, mentioned in connection with *S. maduræ* does not obtain with this organism. The principal cultural characteristics on various media are shown in the table and may briefly be summarized as follows:

Small, white, irregular, round, raised, opaque colonies develop on *ordinary agar* after two to three days. Growth is slow and not abundant and no pigment is produced.

Glycerine-agar after three days shows discrete colonies which coalesce later and become heaped up, presenting a moist, meal-like growth. No pigment is produced.

On *potato*, growth appears after 48 hours as a buff-yellow, granular, raised mass without pigmentation or erosion of this medium.

In *bouillon* growth appears after 48 hours as a grayish, flocculent mass at the bottom of the tube, later a few grayish granules appear on the surface of the medium and in some instances "puffball" formations occur at the bottom of the tube. The fluid remains clear.

In *ascitic fluid* a very slight growth slowly develops at the bottom of the tube.

In litmus-milk growth appears only at the bottom of the tube. The milk is not coagulated and its color is not changed.

Pathogenicity: This species is an exquisite tissue parasite for monkeys, and is pathogenic to a less extent for some other animals. Monkeys inoculated in the abdominal cavity and killed after five to fifteen days show characteristic lesions. In the majority of instances the early lesions are tubercle-like formations scattered through the mesentery and other tissues contiguous to the point of inoculation. In some cases pus pockets and channels are formed, surrounded by adhesions and containing granules made up of the microörganisms in the pus-like material. Guinea pigs inoculated in a manner similar to the monkeys give parallel results.

No. 8. *Streptothrix eppingeri* "A," and

No. 9. *S. eppingeri* "B." These strains are identical in all essential particulars and may be described under the correct name of *S. eppingeri*. This is one of the most important species of this group of organisms and has been well described several times. It has been isolated from anatomical lesions of such varying character as those from meningitis, by Eppinger and others, to Madura foot, as has been published in our first report. Foulerton has described this species and we have fully discussed its characteristics in our first report and summarized them in the table in this paper. Our work has demonstrated fully the identity of *S. freeri* with this species and it is probable that several of the varieties described in the literature also must be classified with it. Its characteristics may be summarized as follows:

Morphologically a variety of forms exist varying from small, oval, coccus and bacillus-like bodies, to long branching filaments, depending upon the lesion or the age of the culture and the media used. In tissues the branching filaments are not seen by the ordinary method of staining, the growth occurring as a skein of thread-like filaments and with colony formation. The threads present a beaded appearance by using Gram-Weigert's stain. In cultures portions of the filaments are acid-fast by the Ziehl-Neelsen-Gabbett method, and they are also Gram positive. The entire mass from experimental lesions is often acid-fast.

Culturally the species is a facultative aërobe and grows on the majority of media. Growth becomes apparent on ordinary agar after two days, consisting of a smooth, adherent membrane which at first is porcelain-white, later it develops a delicate, orange-pink color. The medium remains moist and is not colored in its depth.

Glycerine-agar, after about three days, shows a growth consisting of small, whitish colonies, which gradually develop a delicate pink color. Later, as the colonies progress, they become umbilicated and coalesce, forming a heaped-up growth and producing a bright, orange color. The medium becomes slightly darkened.

On *potato* the growth appears after about four days as a granular layer, at first white, later becoming yellowish and gradually assuming a brick-red color. As the colonies develop they become umbilicated then coalesce and finally produce a moist, meal-like growth on the surface of the medium. The colonies can be lifted in heaps from the medium by the platinum loop, and when immersed in salt solution or distilled water readily disintegrate into fine, flat particles which float on the surface.

In *bouillon* growth appears after 48 hours in the form of small, flat particles, which at first are white, but later assume an orange tint on the surface of the medium. As growth progresses, the colonies coalesce and produce a membrane on the surface of the liquid. Portions of this membrane fall to the bottom of the tube.

In *ascitic fluid* a very slight growth occurs after six day's incubation.

Litmus-milk shows growth on the surface of the medium in the form of fine, white particles which in time becomes pink in color. A film is gradually formed on the surface of the milk, which is neither coagulated nor changed in color.

Pathogenicity: The three cultures of this species, including the two strains from Foulerton as well as our own, are pathogenic for monkeys, producing on inoculation characteristic progressive lesions. (See animal experiments.) Typical Madura foot may be produced by inoculation into the feet of monkeys. Subcutaneous inoculation produces abscess-like pockets, containing a thick, viscid pus in which the colonies of the organism may be observed as small, white granules. Intra-abdominal inoculation results in tubercle-like formations with adhesions, breaking down of tissue with abscess and sinus formation. Granules made up of the colonies are present in the abscess contents.

No. 10. *S. capræ.* A study of this species from the culture sent us by Foulerton confirms in general the findings of Silberschmidt and of Foulerton. It shows characteristics which differentiate it specifically from any of the others with which we have worked.

Morphologically this organism more closely resembles the bacteria than the others and in its action on monkeys it also resembles the tubercle bacillus quite closely. The filaments show true branching without club formation and they are shorter than with most of the other species. Bacillus- and coccus-like forms predominate in cultures and are also very prevalent in experimental lesions. It stains by the stronger aniline dyes in a somewhat irregular manner, is Gram positive and largely and strongly acid and alcohol fast.

Culturally it is a facultative aërobe and grows on most of the laboratory media. Growth first becomes apparent in from two to four days and progresses slowly. The cultural characteristics are shown in the accompanying table and need not be repeated here.

Pathogenicity: This organism is pathogenic for monkeys and guinea pigs and by intraperitoneal injection for rabbits. The lesions differ somewhat from some of the other members of the group in that there is much less tendency to suppuration or other form of tissue necrosis. The lesion is essentially a tubercle-like formation which spreads from the point of inoculation by the formation of other small granules. When studied microscopically these lesions resemble the tubercle quite closely, always contain the microörganism and occasionally giant cells are encountered. The tubercle-like granules occasionally break down and form small pockets of thick granular pus-like material, but this is the exception and granules made up of colonies of the parasite have not been encountered as in the other species.

No. 11. *S. canis.* This organism is probably identical with *S. capræ* of Silberschmidt. The only important points of difference in the cultures which we have are shown in the table, and consist principally in the difference in reaction in litmus milk. Morphologically and in its pathogenic action *S. canis* gives very similar results to *S. capræ*. The same tubercle-like lesions are formed in experimental animals and the close similarity in other respects has led to the conclusion that the two belong to a single species.

No. 12. *S. chalcea.* This is a nonpathogenic species reported by Foulerton and carried along in this work principally as a control. It is distinguished specifically from the other species by morphologic and cultural characteristics, and particularly by its being nonpathogenic for monkeys.

ANIMAL EXPERIMENTS.

The following are summaries of our animal experiments. The general results are placed under the discussion of the characteristics of the various species of the microörganisms. A complete summary will be found in the chapter on general discussion and conclusions.

S. nocardi:

Monkey No. 3635, inoculated in the abdominal cavity with one loop of a two months' culture and the animal killed 12 days later. Autopsy shows numerous miliary tubercle-like granules extending over the entire surface of the omentum and mesentery with an occasional suppurative process. The pus when pressed out contains small, yellowish-white granules made up almost entirely of the microörganism.

Monkeys numbered 3722, 3726, 3714 were inoculated in a similar manner to the above. All showed similar lesions with the exception of monkey No. 3722 which gave a negative result.

Guinea pigs and rabbits inoculated in the abdonimal cavity for the greater part developed similar lesions. Intravenous inoculation in rabbits gave negative results.

S. eppingeri:

Monkey No. 3665 was inoculated in the abdominal cavity with one loop of a ten days' culture and the animal was killed thirteen days later. Autopsy shows numerous, tubercle-like granules in the lower portion of the mesentery, with extensive adhesions of the mesentery to the abdominal wall. On separating the adhesions, or on section through them, numerous sinusses are exposed; these hold a thick, viscid, pus-like substance containing numerous small grayish-white granules composed principally of *Streptothrix*.

Monkeys numbered 3664, 3633, 3622 were inoculated in a similar manner to monkey No. 3665 and the lesions produced were in all essentials similar to those found in that animal.

Foulerton's strain of S. eppingeri.

Monkey No. 3725 was inoculated in the abdominal cavity with one loop of a ten days' culture and the lesions produced are similar to those found in animals inoculated with *S. eppingeri* of the original strain.

S. maduræ.

Monkey No. 3854 was inoculated by opening the abdominal cavity and burying a loop of the material from a two weeks' culture of Strong's strain of the organism. Ten days later the animal presented a distended abdomen with a marked tympanites and was killed on this date. Autopsy shows numerous miliary tubercle-like processes in the omentum and mesentery and adhesions surrounding the inoculated material. The adhesions are easily separated and show small, pinkish-white granules adhering to the mesentery.

Rabbits and guinea pigs inoculated subcutaneously, intravenously, and intraperitoneally with this organism gave negative results.

Monkey No. 3856 was inoculated in the abdominal cavity with one loop of a two weeks' culture of Fullerton's strain of this organism and killed two weeks later. Autopsy shows a small, tumor-like mass made up largely of adhesions confined to the coils of the intestine, omentum, and abdominal wall. On section the tumor shows several small abscesses from which can be expressed a thick pus containing small, white granules composed almost entirely of the organisms. The latter are present in large numbers.

Monkey No. 3724 was inoculated in a manner similar to the above with negative results.

Guinea pig No. 3856 was inoculated into the abdominal cavity with one loop of a two weeks' culture and killed after 10 days. Autopsy shows slight adhesions of the omentum to the abdominal wall and intestine, but no other lesions are present.

Subcutaneous and intravenous inoculations of monkeys, rabbits, and guinea pigs gave negative results in every case.

Monkeys numbered 3719, 3627, 3668 were inoculated with one loop of a two weeks' culture of Vincent's original strain of this organism. The inoculations were made subcutaneously and intraperitoneally and in no instance were progressive lesions produced.

Guinea pigs and rabbits inoculated subcutaneously, intravenously, and by intraperitoneal injections also gave negative results.

Actinomyces (from the Pasteur Institute):

Monkey No. 3864 was inoculated into the abdominal cavity with one loop of a two weeks' culture. The animal died three weeks later. Autopsy shows small abscesses in the abdominal wall at the site of inoculation and numerous miliary, tubercle-like granules in the omentum and mesentery. The pus from the abscesses contains many minute, hard, black granules which by microscopic examination are seen to be made up of a net-work of mycelia and transformation products of the microörganism.

Monkeys numbered 3622 and 3623 were inoculated in a similar manner and presented similar lesions to the above. Intravenous, subcutaneous, and intraperitoneal inoculation of rabbits and guinea pigs gave negative results in each case.

S. capræ:

Monkey No. 3858 was inoculated into the abdominal cavity with one loop of a two weeks' culture and ten days later the animal was killed. Autopsy shows numerous miliary, tubercle-like bodies on the mesentery, diaphragm, and on the surface of the liver. There is slight adhesion of the omentum to the abdominal wall at the site of the inoculation.

Monkey No. 3625 was inoculated into the subcutaneous tissue and into the peritoneal cavity with a suspension of this organism. The animal died three weeks later. Autopsy shows extensive adhesions around the site of inoculation and there is a large abcess in the abdominal wall. On section the abcess contains a heavy, creamy, pus-like material in which are numerous, minute, grayish-white granules. These granules are composed of microörganisms and a pure culture is easily obtained by transplanting the granules to artificial media.

Guinea pig No. 3859 was inoculated in a similar manner as were monkeys numbered 3858 and 3625 and the lesions produced were similar to those described for the monkeys. Intravenous inoculations of rabbits gave negative results in the animals used.

S. canis:

Monkeys numbered 3633 and 3626 were inoculated in the abdominal cavity with one loop of a two weeks' culture and a two months' culture of this organism' respectively, and both animals were killed two weeks later. Autopsy shows slight adhesions near the site of inoculation. The omentum and mesentery are intensely congested and contain numerous miliary, tubercle-like granules.

Monkeys, guinea pigs, and rabbits inoculated subcutaneously showed no progressive lesions at autopsy. Intravenous inoculation of rabbits gave negative results. Intraperitoneal inoculation of guinea pigs in two instances produced lesions similar to those described for intraabdominal inoculations in monkeys.

S. chalcea.

Monkeys, guinea pigs, and rabbits when inoculated subcutaneously and intraperitoneally gave negative results.

LITERATURE.

A review of the literature of this subject may for convenience be divided into two divisions (1) *genus* and (2) *species* determinations.

Several of the generic names which have been introduced are clearly descriptive of organisms belonging to other genera such as *Cladothrix* or *Leptothrix,* and some refer to organisms properly belonging to the classes *Oïdia* or *Bacteria.*

GENUS.

The generic names which appear to have some claim for consideration are as follows:

STREPTOTHRIX.

Corda named this genus, giving, according to Saccardo (Sylloge Fungorum (1886), 4, 282) the following generic diagnosis:

"Hyphæ fertiles erectæ, virgato-ramosæ, ramis ramulisque spiraliter tortis. Conidia globosa v. ovoidea, in ramulis solitarie acrogena, subinde pleurogena, sessilia v. stipitellata, fusca."

Cohn (Untersuchungen über Bacterien, II.—Beiträge zur Biologie der Pflanzen (1875), 1, 186) used the name *Streptothrix* in a new sense in describing an organism *Streptothrix fosteri,* which he found in the lachrymal ducts of a patient. The definition for this organism as given by De Toni and Trevisan (Saccardo's Sylloge Fungorum (1889), **8**, 928) is as follows:

"Filamentis tenuissimis, hyalinis, parallele insimul stratiformi-coalitis vel fasciculatis, rectis vel incurvis, sparse irregulariterque ramosis, in fragmenta inaequilia secedentibus."

CLADOTHRIX.

Cohn (*loc. cit.*, 185) under the name *Cladothrix dichotama* described an organism which was later included as the type species of a genus established by Marchand (Botanique cryptogamique, Paris (1883)) of which De Toni and Trevisan (Saccardo, (1889), **8**, 927) give the following generic diagnosis:

"Filamenta basi ab apice superiore distincta, vagina crassa obducta cylindrica, ætate provecta a basi ad apicem magis magisque incrassata, articulata, pseudoramosa. Arthrosporae binae in singulis microbaculis ellipsoideis ortae."

However Mace (*Compt. rend. acad. sci.* (1888), **106**) in a careful study of *Cladothrix dichotoma* Cohn showed that it did not have the supposed property of dichotomous division of the filaments, but that this appearance was simulated by a lateral branching process.

ACTINOMYCES.

Meyen (Linnæa (1827) **2**, 433) described a fungus under the name *Actinomyces horkelii.* Bollinger (*Centrabl. f. d. med. Wiss.* (1877), **15**, 481) published an account of a disease in cattle caused by a vegetable organism which was carefully described and named *Actinomyces* by Harz (*Jahresb. d. k. Central-Thierarzneischule,* München (1877–78), who at this time probably did not know of the previous occupation of the name by Meyen.

The work of Bollinger and Harz attracted much attention and was rapidly followed by a number of important contributions to the subject. For example, James Israel (*Virch. Arch.* (1878), **74**, 15; 50) described a similar organism as the cause of a similar disease in man and Ponfick (*Breslauer ärtzliche Zeitschrift,* May, 1879, and in subsequent publications) established the generic identity of the microörganisms in man and animals. The work of several writers showed that there existed varieties of this organism, but for a considerable time *Actinomyces* remained unquestioned as a generic name for the organisms.

Botanists classified the organisms in various ways, the most noteworthy being that of De Toni and Trevisan who created a new genus *Nocardia* (Saccardo, **8**, 927) and placed *Actinomyces* (Saccardo, **8**, 928) as a species with the following diagnosis:

"Glomerulis subglobulosis e filamentis densissime intertextis, fasciculos innumeros apice valde incrassato clavatos, a puncto centrali communi undique irradiantes constitutis."

OÖSPORA.

This generic name was introduced by Sauvageau and Radais (*Ann. Inst. Pasteur* (1892), **6**) to include the organisms previously described as *Actinomyces, Cladothrix,* and *Streptothrix.* This term never was seriously considered in the literature and needs no further notice.

NOCARDIA.

De Toni and Trevisan (Saccardo, **8**, 927) introduced *Nocardia* as the generic name and included as synonyms, *Streptothrix Actinomyces*, and in part *Discomyces*. The generic diagnosis given by them is as follows:

"Filamenta tenuissima, evaginata, articulata, Cladotricis more pseudoramosa, nunc e nucleo firmo radialiter expansa, nunc varie coalita. Arthrosporae in filamentis normalibus obvenientes, transformatione cocci singuli ortæ.—Est *Cladothrix* sine vaginis.

SPHÆROTILUS.

Engler (Syllabus der Pflanzenfamilien (1907), 5 ed., 5) places all the above-described organisms in the family *Chlamydobacteriaceae* of the *Schizomycetes*. He reduces the above-mentioned genera including *Actinomyces* to *Sphaerotilus* Kuetz (1833) the generic definition of which as given by De Toni and Trevisan (Saccardo, **8**, 926) is as follows:

"Filamenta premitus affixa, basi ab apice superiori distincta, initio simplicia, dein Cladotricis more pseudoramosa a basi ad apicem subæquilata, articulata, vagina gelatinosa obducta, in fasciculos crassos floccosos varie divisos consociata. Multiplicatio fragmentis filamentorum secedentibus, quae filamenta et fasciculos novos efficiunt. Arthrosporae numerosissimae, articulorum divisiones in tres directiones ortæ."

The above review shows the confusion which exists regarding the botany of the group of organisms which are variously recognized as *Streptothrix, Cladothrix, Actinomyces, Nocardia,* etc., and this seems to have been still further emphasized by workers in medicine and by other recent writers upon the subject. Some of the more important contributions are as follows:

Petruschky (Handbuch der Microörganismen, Kolle and Wassermann (1903), **2**, 832) classifies *Actinomyces, Streptothrix, Cladothrix* and *Leptothrix* as species of *Trichomyceta* of the *hyphomycetes*. He recognizes *Streptothrix* as the generic name of the parasites of mycetoma.

From the standpoint of an investigator in medicine, whatever may be the criticisms of botanists, the work of L. Gedoelst (Les Champignons parasites de l'homme et des animaux domestique, Paris, 1902) is particularly satisfactory, because of its simplicity of arrangement and attention to details. His classification places the organism under discussion among the *Fungi imperfecti* and in the genus *Discomyces* Rivolta (1878), with *Streptothrix* Cohn (1875); *Actinomyces* Harz (1877); *Nocardia* Trevisan (1889); *Oöspora* Sauvageau et Radais (1892) and *Discomyces* Blanchard (1900) as synonyms.

Foulerton (Allbutt's System of Medicine (1906), **2**, pt. 1, 302) who has been interested in this subject and has made many most important contributions to it, maintains *Streptothrix* Cohn to be the generic name. Foulerton gives four reasons for using *Streptothrix* in preference to any of the other terms.

1. He does not consider that Corda's indefinite use of the term in 1833 should make *Streptothrix* Cohn (1875) untenable.
2. This being acceptable, *Streptothrix* becomes the correct botanical name by priority of description.
3. *Streptothrix* was adopted by the committee of the Pathological Society.
4. It is by far the most generally used name.

James Homer Wright (Osler's Modern Medicine (1907), 1, 327; 340) who has made valuable contributions to the study of *Actinomycosis* recognized *Nocardia* as the correct generic name, but raises Actinomyces from species, as given by Trevisan, to generic rank and thus converts what most authors have included in a single genus, into two genera.

Sir Patrick Manson (Tropical Diseases (1907), 4 ed., 759) in his recent discussion of mycetoma has adopted a liberal etiologic classification, both by his definition and his classification of the varieties of mycetoma. He classes actinomycosis as one variety of mycetoma, designating it as actinomycotic mycetoma, and the other names under discussion here might also be included in this category, if we adopt this definition. This eminent author in his definition of mycetoma terms it "a fungus disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body."

Manson in this classification follows Brumpt (*Arch. Parasit.* (1906), 10, 489) who in turn apparently adopts his classification of the parasites from Gedoelst (*loc. cit.*). The diverse forms of the disease recognized are:

I. Actinomycotic mycetoma caused by *Discomyces bovis* (Harz 1877). II. Vincent's white mycetoma produced by *Discomyces maduræ* (Vincent 1894). III. Nicolle's white mycetoma the result of *Aspergillus nidulans* (Eidam 1883). IV. Buffard's black mycetoma caused by *Aspergillus bouffardi* (Brumpt 1906). V. Classic black mycetoma from *Madurella mycetomi* (Laveran 1902). VI. Brumpt's white mycetoma from *Indiella mansoni* (Brumpt 1906). VII. Reynier's white mycetoma resulting from *Indiella reynieri* (Brumpt 1906). VIII. Bouffard's white mycetoma from *Indiella somaliensis* (Brumpt 1906).

SPECIES CONSIDERATION.

Following the generic name of the entire group of organisms under consideration, the next logical step of the problem is a discussion of the species properly belonging to the genus.

The classification of species is a more difficult problem than the generic determination, largely because of the imperfect description of many of the so-called species or varieties. In fact, but few have been described with sufficient clearness to make determination possible.

It is not possible to state who first recognized this group of organisms. It may have been Corda, 1842; Mayen, 1827; Von Langenbeck, 1845 (Acland in Allbutt's System (1906), 2, pt. 1, 325); Sir T. Smith, 1855 (*ibid*); Lebert (1857) (Traité d'anatomie pathologique, 1, 54); Ballingal, 1855; or any one of several other writers, some of whom undoubtedly saw these parasites in lesions of the human body.

However, Henry Vandyke Carter, working from 1859 to 1874, first established the pathogenic rôle of the streptothrices in human pathology. While Carter did not cultivate his organism on artificial media and his descriptions are insufficient for species determination, a study of his publications leaves no doubt but that he was working with a clinical type of *Streptothrix* infection and his observations as to the specific etiology were quite satisfactory.

Erye 1860, Collas 1861, Biddie 1862, Coquerel 1866 Moxon and Hogg (*Trans. Path. Soc.*, London (1870)), Bristowe (*Trans. Path. Soc.*, London (1871)), Hogg (*Med. Times & Gaz.*) (1871), all recognized fungus-like bodies in cases of foot infection, which were clinically mycetoma or Madura foot.

Berkeley (*Med. Press & Circ.*, (1876)) states that he had cultivated one of these organisms from a case of Madura foot which had been forwarded to him by Vandyke Carter. He named the organism *Chionyphe carteri.*

Rivolta (*Med. Vet.* (1868)) probably saw these organisms in pus taken from an abscess on the jaw of a cow. Rivolta (1868–1875) also found disc-like bodies in nodular masses from the tongue of a cow. He named the disease sarcomycosis.

Robin (Traité de Microscopie, Paris (1871), 575) gives a brief description of yellowish granules from two abscesses which were probably due to *Streptothrix* infection.

Heller (about 1872, completed a work which he published in *Deutsch. Arch f. klin. Med* (1885), **37**, 372) and from his description and drawing probably saw these organisms in the discharges from a case which he later considered to be acute actinomycosis.

Perroncito (1875) evidently saw and described species of this organism taken from a pseudosarcoma of the jaw of a cow.

Cohn (*Beitr. Biol. d. Pflanzen.* (1875)) **1**, 148, described an organism which he obtained from concretions in the lachrymal canals of a patient, terming it *Cladothrix fosteri.*

Bollinger (*Deutsche Ztsch. f. Thiermed.*, Leipz. (1877), **3**, 334) noted the constant occurrence of a branching organism in lumpy-jaw of cattle; Harz (*ibid*, (1878)) described it, naming the organism *Actinomyces bovis* and Bollinger termed the disease actinomycosis.

Israel (*Virch. Arch* (1878), **74**, 15) described a disease in man similar to actinomycosis in cattle and detailed the microscopic appearances of the causative *Streptothrix.* Ponfick (*Breslau. ärztl. Ztschr.* (1879) furnished strong evidence of the etiologic identity of the diseases of man as described by Israel and of cattle as given by Bollinger and Harz.

Corre (*Arch. méd. Nav., Par.* (1883)) in reporting the notes of Dr. Collas called attention to the probable identity of actinomycosis with the earlier described mycetoma, and many other authors since that time have come to the conclusion that the diseases are probably the same.

Mandareau (*Bull. acad. méd.* (1887), **18**, 555) gave a morphologic description of a species of *Streptothrix.* Nocard (*Ann. Inst. Pasteur* (1888), **2**, 293) described and cultivated a *Streptothrix* from the lesions of a disease known as *farcin du boeuf* which was very prevalent among cattle in Guadeloupe. Organisms which agree with Nocard's description have repeatedly been isolated from pathologic lesions by other authors. Nocard's work was epoch making in that he was the first satisfactorily to cultivate a *Streptothrix* in pure culture.

Affanassiew and Schultz (*Münchener med. Wchnsch.* (1889), **36**, 418) briefly described a *Streptothrix* obtained from pus and sputum. Cultures were pathogenic for guinea pigs. Protopopoff and Hammer (*Ztschr. f. Heilk.* (1890, **11**, 255) reported incomplete studies of the cultures of Affanassiew's and Schultz's organism. Kischensky (*Arch. f. exp. Path. u. Pharm.* (1889), **26**, 79) partially described and probably cultivated a *Streptothrix* which may have been identical with that cultivated later by Wolff and Israel from a human case of actinomycosis of the lungs. Bujwid (*Centrbl. f. Bakt., etc. Abth.* 1 (1889), **6**, 630) cultivated and briefly described a *Streptothrix* which was a facultative anaërobe taken from a human case of actinomycosis.

Eppinger (*Wien klin. Wchnsch.* (1890), **3**, 321) cultivated a *Streptothrix* from a brain abscess and a "pseudo tuberculosis of the lungs", the patient having manifested the clinical symptoms of meningitis during life. This organism was Gram positive, acid-fast and a facultative aërobe. Growth occurred on the ordinary laboratory media and the organism was pathogenic for laboratory animals. Eppinger's publication, like that of Nocard, forms a landmark in the history of the disease. His work has been confirmed by MacCallum and others and his organism, which is a different species from that of Nocard, will be more fully considered in this paper.

Almquist (*Ztschr. f. Hyg.* (1890), **8**, 189) cultivated species of *Streptothrix* from three different sources. The first was discovered as a contamination in a gelatin culture tube, the second was cultivated from pus taken from the base of the brain from a human case and the third culture was isolated from water. Liebman (*Arch. per le sci. med.* (1890), **14**, 361) discussed the cultivation of *Streptothrix* in pure culture.

Bostroem (*Beitr. z. path. Anat., etc.* (1891), **9**, 1 to 240) cultivated a single species of *Streptothrix* from eleven cases of actinomycosis. His organism was Gram positive and in part acid-fast and was a facultative aërobe in cultures. Growth was obtained with difficulty directly from the lesions, but the later transplants were more satisfactory in artificial media. Bostroem's article was the first published exhaustive consideration of the cultivation of *Streptothrix*. Wolff and Israel 1891 (*Virch Arch.* (1891), **126**, 11) cultivated a *Streptothrix* from two cases of clinical actinomycosis in man. In one case the lesion was a retromaxillary tumor and the other was actinomycosis of the lungs. This organism was acid-fast and a facultative anaërobe. Gruber (*Tr. VII Intern. Cong. Hyg. & Demog.*, Lond. (1891), **2**, 65) discovered (as an accidental contamination of culture media) an organism which he described as *Micromyces hofmanni*. This organism produced pyæmia in animals and "ray fungus" types were present in the lesions. The articles by Doyen (*Tr. VII Intern. Cong. Hyg. & Demog.*, Lond. (1891), **3**) and Roussel (These, Paris, 1891) are not available to us.

Hesse (*Deutsche Ztschr. f. Chir.* (1892), **34**, 274) obtained a *Streptothrix* by culture from an abscess in the groin, which when opened was found to communicate by a sinus with the intestine. Autopsy on the patient, who died after more than a year's illness, showed a rectal fistula communicating with multiple abscesses in and around the pelvis. There was bronchitis, but the organisms were not found in the sputum. The organism was Gram positive and aërobic in culture media. Growth occurred on the majority of media and serum media were liquefied. No positive results were obtained from intravenous, intraperitoneal, or subcutaneous injections of cultures into rabbits, guinea pigs or white mice. Sauvageau and Radais (*Ann. Inst. Pasteur* (1892), **6**, 242) studied a number of streptothrices which had already been isolated by other authors. They made a classification of *Streptothricae* in general, based upon cultural characteristics.

The articles by Lanz (*Cor. Bl. f. schweiz. Aerzte* (1892), 307; 339); Ebermann (Inaug. Diss. St. Petersburg (1893); Dor (*Gaz. hebd. de med.* (1893) 2 s., **30**, 40) and of Dor and Bérard (*Prov. méd.* (1893) are not available to us.

Vincent (*Ann. Inst. Pasteur* (1894), **8**, 129) cultivated a *Streptothrix* which was pathogenic for laboratory animals from a case of ochroid variety of mycetoma. We have already noticed this organism somewhat in detail and it will be considered further. Vincent's work is very important because he was the first satisfactorily to cultivate a *Streptothrix* from the Madura foot type of the disease and because his organism is specifically different from any of those described before his paper appeared. Boyce and Surveyor (see bibliography) in a series of articles, described streptothrices which they were able to isolate from cultures made by friends in India, taken from cases of mycetoma and forwarded to the authors in England. The brief description given by these authors renders it probable that this organism was identical with that of Vincent. Karg (Ref. Düms' *Deutsche mil-ärztl. Ztschr.* (1894), **23**, 145) cultivated a *Streptothrix* from a case of actinomycosis in man. Karg considered his organism to be identical with that of Bostroem. This author also reported a second case of the disease with results similar to those obtained with the first one. Leith (*Edinb. Hosp. Rep.* (1894), **2**, 121) and Newjadomsky (Ref. Lubarsch and Ostertag Ergb. (1898), **5**, 665) each isolated by culture a *Streptothrix* from a human case of actinomycosis. The article of Kitchensky (*Arch. f. exper. Path. u. Pharmakol.* (1890), **26**, 79) is not available to us. Sabrazès and Rivière (*Presse méd.* (1894), Sept. 22) reported the cultivation of a *Streptothrix* from abscesses in the brain, lungs, and kidneys of a human case. This organism only grew anaërobically. In their second case (*Mercredi méd.* (1895), 485) an aërobic *Streptothrix* was cultivated from the sputum and subcutaneous abscesses of a patient. Both these organisms are reported as being pathogenic for small animals, the latter one, however, only producing lesions when injected together with dilute acetic acid.

Aschoff (*Ber. klin. Wchnsch.* (1895), **32**, 738) cultivated a *Streptothrix* from a case of human actinomycosis and stated that he had produced actinomycotic lesions in animals by inoculating cultures of the organism.

Du Bois Saint-Sevrin (*Semaine méd.* (1895)) cultivated a *Streptothrix* from a case of ulcer of the cornea in a human patient with a pseudomembranous conjunctivitis. Ferré and Faguet (*Mercredi méd.* (1895), 441) did the same from an abscess in the *centrum ovale* of the brain. The authors considered this organism to be identical with that of Eppinger. Rullmann (Ref. *Centralbl. f. Bakt., etc.* (1895), **17**, 884) cultivated a *Streptothrix* from soil and again in 1898 the same author (*Münchener med. Wchnsch.* (1898), **45**, 919) cultivated what he apparently considered to be the same organism from a case of disease of the lung. It was a *Streptothrix* positive to Gram's stain, which grew on ordinary media as a facultative aërobe. Positive local lesions were produced in rabbits, guinea pigs, and mice when these animals were inoculated with cultures. Garten (*Deutsche Ztschr. f. Chir.* (1895), **41**, 257) cultivated a *Streptothrix* from lesions in a human case. There was necrosis of the vertebrae and ribs, with abscesses, sinus formation and empyæma. This organism grew on laboratory media and was pathogenic for three out of thirty-seven rabbits and guinea pigs.

Dor (*Gaz. hebd. d. méd.* (1896), **43**, 553) obtained a *Streptothrix* from an actinomycosis-like abscess at the angle of the jaw. The pus contained granules with long, beaded filaments which did not stain by Gram's method. The organism grew aërobically on liquid media only. Sawtschenko (*Baumgarten's Jahresb.* (1896), **12**, 613) cultivated an organism from a case which he termed pseudoactinomycosis. It formed long threads which did not stain by Gram's method and which grew only under anaërobic conditions. Jurinka (*Mitth. a. d. Grenzgeb. d. Med. u. Chir.* (1896), **1**, 139) cultivated a *Streptothrix* from a human case of actinomycosis which he considered identical with that of Wolff and Israel. The article by Kozerski (Ref. *Jahresb. d. ges. Med.* (1896), **2**, 223) is not available to us.

Scheele and Petruschky (*Verhandl. d. Con. f. innere Med.* (1897), **15**, 550) cultivated a *Streptothrix* which was acid-fast by the Ziehl-Neelsen method from the sputum and subcutaneous abscesses of a case of pyæmia, pleuro-pneumonia, cystitis, and pyelitis. It grew on agar, gelatin, and broth. Its pathogenic character for animals apparently was not determined. Buchholtz (*Ztschr. f. Hyg.* (1897), **24**, 470) described a *Streptothrix* found in the lung of a patient suffering from a disease which, both clinically and pathologically, very closely resembled tuberculosis of the lungs. The organism was Gram positive and acid-fast, but did not grow on artificial media. Urban (*Münchener med.*

Wchnsch. (1897), **44**, 124) cultivated a *Streptothrix* from a case of human actinomycosis. Berestnew (Aktinomykose und ihre Erreger (Dissert), Moskau (1897) reported several cases. A *Streptothrix* was cultivated from a subperiostial abscess of the lower jaw of a woman (Case I). This clinically was a case of "lumpy jaw." This organism was a *Streptothrix*, facultative anaërobic, Gram positive, dying after three generations on artificial media. It was not pathogenic for rabbits, guinea pigs, or tame mice. The organism from his Case II was cultivated from an abscess under the right nipple of a 16-year-old patient who had symptoms of disease of both lungs. The organism differed from that of Case I in that it grew somewhat better in the presence of oxygen. The cultures in Case III were from sputum and chest sinuses in a patient forty-four years of age, who died after an illness of about one year. The organism was Gram positive, facultative aërobic, and grew best in bouillon. It was neither fatal for rabbits nor guinea pigs when injected either intraperitoneally or subcutaneously; a temporary infiltration of the tissues resulted by the latter method. Abel (*Münchener med. Wchnsch.* (1897), **44**, 124; 149) made brief reports of a pathogenic *Streptothrix* from sputum. Van Neissen (*Virch. Arch.* (1897), **150**, 482) worked with an organism which was not differentiated from that of Wolff and Israel.

Berestnew in another case (*Ztschr. f. Hyg. u. Infectionskrankh.* (1898), **29**, 94) obtained a *Streptothrix* in pure culture from the lesions in a child suffering from an abscess of the lung and pyæmia. This organism was negative to Gram, grew anaërobically on media and was pathogenic for animals. Petruschky (*Deutsche med. Wchnsch.* (1898), **24**, Ver.-Beil. 78) cultivated an organism similar to that of Scheele and Petruschky (*loc. cit.*) from the sputum obtained from a second case of streptothricosis. Alissow and Skworzow (ref. Lubarsch and Ostertag (1898), **5**, 664) studied two cases of streptothricosis in man. They obtained two organisms in bouillon cultures, a bacillus and a *Streptothrix* growing in symbiosis. Pure cultures of the *Streptothrix* developed only clubs and rods, but when bacteria were again mixed in the cultures, long fungus threads were produced. The authors consider the lesions to be due to the mixed infection. Schtscheglow (1898) (*ibid.*), also secured mixed cultures and the bacteria present influenced the morphology of the *Actinomyces*. Newjadomsky (1898) (*ibid*) reported one case in man in which a *Streptothrix* was obtained in pure culture from a subdiaphragmatic abscess. The author considered the organism to belong to a new species. It was not pathogenic for guinea pigs. Rullman (*Münchener med. Wchnsch.* (1898), **45**, 919) cultivated a *Steptothrix* from the sputum of a patient with a localized lesion near the root of the right lung. This organism was Gram positive and grew on all media. It was pathogenic for mice, rabbits and guinea pigs, and could be reclaimed by culture from lesions in these animals. Grillo (*Reforma Medica* (1898), **14**, 301) cultivated a *Streptothrix* from a case of human actinomycosis and from the bovine infection and reproduced the disease by animal inoculation with cultures of the organism. Harbitz (*Norsk Mag. f. Lægevidensk* (1898), **13**, 1) obtained a *Streptothrix* by culture from five cases of human actinomycosis. Flexner (*Journ. Exp. Med.* (1898), **3**, 435) reports a case of human infection with a *Streptothrix*, but his organism did not grow on artificial media. The article by Marwedel (*Beit. z. klin. Chir.* (1898), **21**, 561) is not available to us.

Foulerton (*Lancet* (1899), **2**, 779) cultivated his *Streptothrix hominis* from abscesses of the chest with deep sinuses in a patient showing symptoms of a severe lung involvent with pyæmic symptoms. This author (see bibliography) has also made numerous other contributions to the morphology of the subject and has probably done more than any other toward clearing up the confusion which exists regarding this group of organisms. Levy (*Centralbl. f. Bakt., etc.* (1899), **26,** 1) cultivated a *Streptothrix* from five cases of clinical actinomycosis in man. He considers his organism to be identical with that of Wolf and Israel. Paul Krause (*Centralbl. f. Bakt., etc.* (1899), **26,** 209) obtained a *Streptothrix* from an abscess of the lower jaw. It was Gram positive but not acid-fast, a facultative aërobe and grew on ordinary laboratory media. No positive results were obtained by intraperitoneal or subcutaneous injection of cultures into rabbits, guinea pigs, or white mice. Hayo Bruns (*Centralbl. f. Bakt., etc.* (1899), **26,** 11) cultivated a *Streptothrix* from a lesion which according to the diagnosis was an actinomycotic abscess of the abdominal wall. The organism was Gram positive, but not acid-fast and did not stain well with the ordinary aniline dyes. Growth occurred on ordinary media, best under aërobic conditions. No lesions were produced by intravenous, intraperitoneal, nor subcutaneous injections of cultures in rabbits, guinea pigs, or mice. Silberschmidt (*Ann. Inst. Pasteur* (1899), **13,** 841) obtained a *Streptothrix* by culture from the lungs of a goat which had a disease closely resembling tuberculosis. This organism was carefully described by the author and later by Foulerton and Jones, (*Tr. Path. Soc.* (1902), **53,** 99) who considered it to be a new species and our work is in accord with this conclusion.

Brault (*Arch. d. parasit.* (1899), **2,** 535) observed two human cases of actinomycosis. He cultivated a *Streptothrix,* at first in symbiosis with bacteria and later in pure cultures. His organism grew on ordinary media and was pathogenic for animals.

Norris and Larkin (*Journ. Exp. Med.* (1900), **5,** 155) obtained a *Streptothrix* by culture from two cases of bronchopneumonia and bronchiectiasis. Both cases proved fatal. This organism was Gram positive, but not acid-fast by the Ziehl-Neelsen method. The authors consider it probably to be identical with Israel's *Streptothrix.* Local lesions were produced in both rabbits and guinea pigs by injection of the cultures. Cozzolino (*Ztschr. f. Hyg. u. Infectionskranfh.* (1900), **33,** 36) reports a human case of *Streptothrix* infection of the ear. He cultivated an organism from the lesion which was pathogenic for mice and guinea pigs and described it very well. It was a facultative aërobe, but branching was not observed.

Dean (*Tr. Path. Soc.* (1900), **51,** 25) cultivated a *Streptothrix* from the lesions in a horse which clinically was suffering from actinomycosis. He considered his organism to be a new species, differing in certain particulars from any described previously. This organism was a facultative aërobe, Gram positive, and grew very poorly on the majority of media and not at all on others. It was pathogenic for animals, producing lesions which contained organisms resembling *Actinomyces,* with club-shaped ends. However, in cultures no club formations were observed. Tusini (*Arch. f. klin. Chir.* (1900), **62,** 249) observed four cases of *Streptothrix* infection in man. The one reported in detail was an infection which clinically was Madura foot. From this case, he cultivated a *Streptothrix* which was pathogenic for guinea pigs and which in cultural characteristics closely resembled the organism of Vincent. Sternburg (*Wien. klin Wchnsch.* (1900), **13,** 548) cultivated a *Streptothrix* resembling that of Wolff and Israel from three cases of human actinomycosis.

Aoyoma and Miyamoto (*Mitth. a. d. med. Fac. d. k. jap. Univ. a. Tokio* (1901), **4,** 231 to 276) obtained a *Streptothrix* in pure culture from an abscess of the lung. This was Gram positive, acid-fast, and a facultative aërobe; pathogenic for rabbits, white mice, and hens. The authors believed their organism to be very closely related to or identical with *S. eppingeri.* Mertens (*Centralbl. f. Bakt., etc.* (1901), **29,** 649) reported one human case and cultivated a *Streptothrix* from the lesions. Cultures at first only grew in bouillon, but gradually growth on other media was successful. The anaërobic tendencies of his organism were changed so that it grew aërobically after a considerable time on artificial media. This organism produced lesions in the eyes of rabbits. Silberschmidt (*Ztschr. f. Hyg. u. Infectionskrankh.* (1901), **37**, 345) studied eight cases of *Streptothrix* infections in man. He cultivated the organism and believed he had isolated three different species. In six of his eight cases the organisms closely resembled those of Wolff and Israel. The others more closely approximate Bostroem's organism. Jelenewski (Ref. *Baumgarten's Jahresb.* (1901), **17**, 495) studied fifty cases of actinomycosis occurring in the mouths of animals. He cultivated the fungus first with *B. subtilis.* Later he obtained pure cultures both aërobically and anaërobically. Cultures of the organisms were pathogenic for calves, but not for rabbits and guinea pigs. The author concluded that his *Streptothrix* was a new species, basing his decision upon both its cultural and pathogenic properties.

Foulerton and Jones (*Tr. Path. Soc.* (1902), **53**, 56) studied the group extensively and described some new species. The tentative classification by these authors was the most satisfactory which had been made up to the time of its publication.

They also cultivated a *Streptothrix* ((ibid), **75**, 93) which they believed to be the cause of the disease, from a conjunctivitis and keratitis in a twelve year old girl. The organism was Gram positive, but not acid-fast; a facultative aërobe growing on all media. It was not pathogenic for rabbits, guinea pigs, or white mice. The same authors (*ibid,* 100) isolated a *Streptothrix* from "a case of pulmonary infection in a woman." This organism was Gram positive, not acid-fast, grew on the usual laboratory media, and was not pathogenic for rabbits. MacCallum (*Centralbl. f. Bakt., etc. orig.* (1902), **31**, 529) cultivated a *Streptothrix* which he considered to be identical with that of Eppinger from the peritoneal exudate in the body of a child dead of subacute purulent peritonitis which followed a surgical operation for relief of stricture of the oesophagus. Birt and Leishman (*Journ. Hyg.* (1902), **2**, 120) studied a *Streptothrix* which was obtained from a fatal human case. Empyæma, pericarditis, and "cirrhotic nodules in the lungs" were present at autopsy. The organism was isolated from the pleuræ, pericardium, and lung. It was Gram positive and acid-fast and showed strong aërobic tendencies. It grew on the majority of media, producing a coral-pink color. This organism was pathogenic for guinea pigs and is probably identical with Eppinger's *Streptothrix.* Schukewitsch (Ref. *Jahresb. d. ges. Med.* (1902), **1**, 711) cultivated a *Streptothrix* somewhat resembling that of Wolff and Israel from twenty-two out of twenty-five cases of human actinomycosis. Von Baracz (*Arch. f. klin. Chir.* (1902), **68**, 1050) reports on fifty-two cases of actinomycosis. The article is a splendid monograph, but does not go extensively into the question of the etiology of the disease. Welleminsky (*Deutsche med. Wchnsch.* (1902), **28**, Ver.-Beil. 196) cultivated a *Streptothrix*-like organism, nonpathogenic for animals, from lesions in one case.

Trolldenier (*Ztschr. f. Thiermed.* (1903), n. s. **7**, 81) reports a case of actinomycosis in a dog. He cultivated a *Streptothrix* which he considered to be a new species from the lesions. The organism was pathogenic for mice and guinea pigs, rabbits, dogs, and calves. Doepke (*Münchener med. Wchnsch.* (1903), **50**, II, 2245) studied several human cases and cultivated organisms which where similar to that of Wolff and Israel. Lignières and Spitz (*Arch. d. parasitol.* (1903), **7**, 428; *Centralbl. f. Bakt., etc.* (1904), **35**, 294; 452) cultivated a *Streptothrix* from a calf suffering from actinomycosis which they considered similar to that of Wolff and Israel. The article by Horst (*Ztschr. f. Heilk., Abt. f. path. anat.* (1903), **24**, 157) is not available to us.

James Homer Wright (*Journ. Med. Research* (1904), 13, 349) cultivated what he believes to be a single species of *Actinomyces* from 13 cases of human actinomycosis and two cases of the bovine disease. He considers his organism to be of the same species, if not identical, with that of Wolff and Israel. This article is the most thorough study of one species of this group of organisms that has yet been made. Stokes (*Am. Journ. Med. Sci.* (1904), n. s. 128, 861) obtained a *Streptothrix* from an abscess of the lung. This organism was acid-fast, grew aërobically and was pathogenic for laboratory animals. Schabad (*Ztschr. f. Hyg.* (1904), 47, 41) considers the true *Actinomyces* and the organisms of Bostroem or Eppinger to be different species. He cultivated from the sputum and abscess of the breast in one human case an organism which he considered to be identical with that of Eppinger in its morphology, biology, and pathogenicity. Hartman (*Tr. Chicago Path. Soc.* (1904), 6, 157) cultivated a *Streptothrix* from one human case. The articles by Tuttle (*Med. and Surg. Rep. Presbyterian Hosp.* N. Y. (1904), 6, 147) and McDonald (*Scot. Med. & Surg. Journ.* (1904), 14, 305) are not available to us.

Pinoy (*Comp. rend. acad. sci.* (1906), 143, 1175) isolated a *Streptothrix* and claimed to have experimentally reproduced the black granules by inoculation of cultures into a pigeon's foot. His organism was a facultative anaërobe. Nicolle and Pinoy (*Arch. d. parasitol.* (1906), 10, 437) cultivated a *Streptothrix* from a case of mycetoma in an Arab.

Musgrave and Clegg (*This Jurnal, Sec. B.* (1907), 2, 477) obtained a culture from the sinuses in a case of the ochroid variety of mycetoma occurring in a Filipino woman in Manila. The cultural characteristics have already been described and will be further discussed. Poppenheimer and Satchwell (*Journ. Infect. Dis.* (1907), 4, 617) report a case of endocarditis and isolation of a pleomorphic bacterium resembling somewhat closely the *Streptothricæ*. They review the literature of *Streptothrix* infections in man and tentatively classify their organism as a *Cladothrix*. The report of these authors is thorough and complete and from their description it does not seem as if their organism could properly be considered under *Streptothricæ*.

Strong cultivated a *Streptothrix* from a case of mycetoma in India. This organism is undoubtedly identical with that of Vincent.

OTHER STREPTOTHRICÆ.

In addition to the pathogenic organisms of the group under discussion and which have been isolated from pathologic lesions in man and animals, others have been cultivated from sputum, pus, or other human excreta under circumstances which make their exact source questionable; there are still others which have only been described as being obtained from animals; and some have been cultivated only from air, water, soil, and other outside sources. The following may be mentioned: *S. rubra* of Ruiz-Casabó (ref. *Centralbl. f. Bakt., etc.* (1895), 17, 466) isolated from sputum; *Cladothrix mordoré* of Thiry (*Arch. d. physiol.* (1897), 29, 284) obtained from an anginal exudate; the *Streptothrix* of Dean (*Tr. Path. Soc.* (1900), 51, 26) isolated from an abscess of the jaw in a horse; and *S. lacertæ* of Terni (ref. *Centralbl. f. Bakt. etc.* (1896), 19, 953) isolated from nodules in the liver of a lizard. Rossi-Doria (*Ann. d. l'Ist. d'ig. sper. d. Univ. di Roma* (1891), 1) cultivated a *Streptothrix* from a case of bovine actinomycosis. Sanfelice (*Centralbl. f. Bakt. etc., orig.* (1904), 36, 355; and *Arch. f. wiss. u. prakt. Thierheil.* (1896), 22, 153) obtained *Streptothricæ* from several minor cases of bovine actinomycosis. He considered his organisms to be similar to those of Gasperini and Doria. Gasperini (*Proc.-verb. Soc. Tosc. di Sci. Nat.* (1895), 9, 64; 292) isolated and described two strains of *Streptothrix* from actinomycosis in cattle. He (*Ann. d. l'Ist. d'ig. sper. d. Univ. di Roma* (1892), 2, 167; *Proc.-verb. Soc.*

Tosc. de. Sci. Nat., July 5, (1896) also worked with a number of cultures obtained from other authors including that of Dessy (*loc. cit.*). With this latter organism, he stated that he had produced typical actinomycosis by injection into the jaw of a cow.

Lange and Manasse (ref. Levy. *Centralbl. f. Bakt. etc.* (1899), **25**, 5) isolated a *Streptothrix* somewhat resembling that of Wolff and Israel from actinomycosis in a dog. Bahr (*Ztschr. f. Thiermed.* (1904), n. s. **8**, 47) cultivated a *Streptothrix* from an actinomycosis-like disease in a dog. Dean (*Tr. Jenner Inst. Prevent. Med.* (1899), **2**, 17) did the same with an organism resembling that of Wolff and Israel, obtained from an abscess in the jaw of a horse and this *Streptothrix* was pathogenic for animals. Mosselmann and Liénaux (*Ann. d. méd. vet.* (1890), **39**, 409) obtained a *Streptothrix* from a case of bovine actinomycosis.

Lignières and Spitz (*Bull. Soc. centr. d. méd. vet.*, Paris (1902), **56**, 487) cultivated a bacillus from cases of clinical actinomycosis in cattle. They state they produced true actinomycosis, the organism showing the club-shaped *Streptothrix* granules, with cultures of this organism, by inoculation of their cultures into cattle.

The *Streptothrix* of Caminiti (*Centralbl. f. Bakt. etc., orig.* (1907), **44**, 193) is one of the most important of the organisms cultivated from the air, because of its pathogenic properties and close cultural resemblances to the *Streptothricæ* which produce clinical actinomycosis. This organism is Gram positive, acid-fast in part, a facultative aërobe with anaërobic preferences, liquefies gelatin and produces pigment in varying amount and color in artificial media. It is pathogenic for all animals experimented upon, producing circumscribed local lesions by injection of cultures.

Other organisms of this class which may be mentioned are *S. leucea* Foulerton (*Tr. Path. Soc.* (1902), **53**, 101) isolated from sewage and water; *S. alpha* Jones (*ibid*, 102); *S. erythrea* Foulerton (*Ibid*, 107) from culture tubes prepared with horse serum; *S. beta* Jones (*ibid*, 109); *Cladothrix invulnerabilis* of Acosta and Grande Rossi (ref. *Centralbl. f. Bakt, etc.* (1893), **14**, 14); the *Streptothrix* of Kedzior (*Arch. f. Hyg.* (1896), **27**, 328) isolated from sewage and water; *S. albido-flava*, *S. carnea*, and *S. aurantiaca* of Rossi-Doria (*Ann. d'Ist. d'ig. d. Roma* (1891), **1**) isolated from air; *Micromyces hoffmanni* described by Gruber (ref. *Centralbl. f. Bakt., etc.* (1891), **10**, 648) isolated from air.

Several other brief descriptions of *Streptothricæ* from pathologic lesions might be noticed, but the principal ones have been mentioned above. The technical descriptions have for the greater part been omitted in this review of the literature, but it may be stated that a classification of this material which will be satisfactory to all is scarcely possible. However, several authors have attemped an arrangement of species and varieties.

Foulerton worked with a large collection of cultures obtained from various sources. He redescribed and renamed several species, both pathogenic and nonpathogenic, the classification being based largely upon morphologic and cultural characteristics. Rossi-Doria occupied himself for the greater part with *Streptothricæ* cultivated from extraneous sources and his classification is based upon the character of the cultures obtained. Gaspereni gave a classification based upon cultural characteristics. Brumpt (*Arch. d. parasitol.* (1906), **10**, 489) recognized several species and more than one genus. Wright worked with one species and gave the most complete description of that organism to be found in literature. His "*Hyphomycete*" cultivated from a case of the "black variety" of mycetoma evidently was not a *Streptothrix* and therefore is not included in the discussion in this paper. Caminiti recognizes forty-one species based upon his own work and a review of the literature. Manson's classification refers particularly to mycetoma and has already been noticed.

If we carefully study the literature of species determination, it will be found in greater part to be only of historic interest and value. The work is generally too incomplete to be final for species determinations, and in cases even the generic position of the described parasites is doubtful. For this reason we have considered only the technical descriptions of the organisms which have been cultivated and described with sufficient accuracy and completeness to make them available for comparative purposes. Much of the work of the older writers was well done when due consideration is given to the technique developed at the time of publication, and this work should always be kept before us in giving historical summaries. However, for purposes of further study and for comparison, having in view the harmonizing of our ideas regarding these infections, it seems to us that the following are the principal publications regarding *Streptothricæ,* which have been isolated from pathologic lesions of man or animals.

1. Nocard (1888); 2. Eppinger (1890); 3. Almquist (1890); 4. Bostroem (1891); 5. Wolff and Israel (1891); 6. Hesse (1892); 7. Vincent (1894); 8. Boyce and Surveyor (1894); 9. Aschoff (1895); 10. Du Bois Saint-Sevrin (1895); 11. Sabrazès and Rivière (1894) (A and B); 12. Rullmann (1895); 13. Dor (1896); 14. Sawtschenko (1896); 15. Scheele and Petruschky (1897); 16. Bucholtz (1897); 17. Berestnew (1897); 18. Rullmann (1898); 19. Silberschmidt (1899); 20. Brault (1899); 21. Cozzolino (1900); 22. Dean (1900); 23. Aoyoma and Miyamoto (1901); 24. Jelenewski (1901); 25. Foulerton (1902) (3 or more species); 26. Trolldenier (1903); 27. Pinoy (1906). The work of Musgrave and Clegg (1907) might also be included in this list.

The twenty-eight species or varieties to be taken from this list are considered with due regard to the manner in which they are described by the authors. It is certain that they do not all represent different species and it is probable that some of the other organisms not included do belong to new species. Many of the articles in the literature are incomplete, and a careful study of such descriptions as are given convinces us that not more than ten different species are represented in the group. Several of the varieties may show slight morphologic and biologic differences, but these are not sufficient to warrant their being classed as separate species.

GENERAL DISCUSSION AND CONCLUSIONS.

The subject of streptothricosis or nocardiosis becomes somewhat simplified if the results of our own work are combined with those taken from the literature, but we realize fully that after considering all possible evidence, points must still remain open for discussion, and complete harmony regarding this subject can only be obtained by common adoption of a somewhat arbitrary classification.

DETERMINATION OF GENUS.

It is difficult to determine upon the correct name of the diseases, because of the botanical confusion regarding the position and designation of the group of organisms concerned, and of the lack of clearness of definition specifying definite limitations for the organisms to be included as the etiologic factor.

Both *Streptothrix* and *Actinomyces* are untenable as generic names if we strictly follow the rules of nomenclature, because they are not entitled to priority in the literature which belongs to *Nocardia;* besides both *Streptothrix* and *Actinomyces* are open to the objection that they have not received a sufficiently clear botanical definition and both names have been used in too uncertain a sense in the past. *Actinomyces* has also, unfortunately, been taken into recent literature with practically two definitions. The objections to *Nocardia* are as follows: (1) The published definition erroneously states that the branching is "false branching;" (2) the name has not been sufficiently accepted by botanists to insure permanency and (3) usage is very much against it, particularly as in some of the recent writings its meaning has been limited to include only a portion of the organisms which surely belong in the genus. Considering the confusion in botanical literature and the uncertainty, and therefore the liability to change which pertains to this nomenclature, we have, as stated in the introduction, chiefly because of usage, and therefore somewhat arbitrarily, tentatively accepted *Streptothrix* as the generic name of the organisms concerned, and streptothricosis as the designation of the disease caused by this group of branching, filamentous organisms. In making this decision we are fully aware of the rights of those who favor *Actinomyces* or *Nocardia,* and under the circumstances are tempted to introduce a new name (*Carterii*) for the genus, together with a full and complete definition.

Whatever the nomenclature, it is a fact that we have here a group of closely allied vegetable parasites of man and animals, which have the following principal characteristics:

Branching, filamentous organisms which develop into colonies made up of the organisms and "transformation products." The terminal hyphæ may or may not be radially placed on the surface of the colony and they may or may not develop "clubs." The group in general take Gram's stain and several members show acid-fast properties in a varying degree.

The organisms grow on artifical media, differing in their requirements for oxygen and in pigment production. To a less degree they show other variations in appearance on artificial media.

The majority of the organisms produce lesions in monkeys, which histologically resemble those found in the human infections and in those of other animal diseases caused by members of this genus.

This group or genus is closely allied to other genera of somewhat similar characters, the latter ranging from the branching bacteria through the nonbranching filamentous *Leptothrix* and the pseudo-branching *Cladothrix*, to the budding *Oïdia* or *Blastomyces*.

The only question of doubt regarding the expediency of our generic classification is raised by the very thorough and exhaustive work of James Homer Wright, who has brought forward some strong arguments in favor of making two genera out of the group of organisms under discussion.

As may be remembered, Wright separates this group into two genera; *Actinomyces* and *Nocardia*. He defines *Actinomyces* accurately and places all the organisms which he thinks do not come within this definition into the genus *Nocardia*.

Actinomycosis is defined as:

> "A suppurative process combined with granulation tissue formation, the pus of which contains characteristic granules of 'drusen' composed of dense aggregates of branched filamentous microörganisms and their transformation of degeneration products. In the term transformation products are included the characteristic, refrangent, club-shaped bodies radially disposed at the periphery of the granule, for these bodies have long since been clearly shown to arise by a transformation of the peripheral filaments. They may or may not be present at the periphery of the granule."

Wright, in his further discussion of the organisms, emphasizes the following points as being characteristic of *Actinomyces*.

Club formation in tissues, anaërobism, granule formation, peculiarities in culture media, morphology and action when injected into laboratory animals. However, some of these distinctions were not constant even in the author's series of cases.

If we accept Wright's definition of actinomycosis, some of the organisms termed *Nocardia* by the author must be included as etiologic factors in actinomycosis, because the requirements are fulfilled by microörganisms not included in his description of the organism which he considers the specific cause of the disease, and furthermore, if his definition and description of *Actinomyces* be accepted as sufficient for genus determination, other genera could be removed from the group with almost, if not with equally good cause. However, some of the principal characteristics given for *Actinomyces* are not peculiar to his organisms. Most of these are differences in *degree only* from other members of the group, and are not specific, and in some instances, as we have demonstrated by work with original cultures, Wright's conclusions, based upon a study of the literature, are wrong. His observations regarding *S. capræ* Silberschmidt, and *S. maduræ* Vincent are examples of this. Wright states that Vincent's case was probably one of actinomycosis, and that Silberschmidt worked with mixed cultures. We have had cultures from the original strains of both these organisms in our hands and are able to state positively that the bacillus- and coccus-like forms of *S. capræ* described by Silberschmidt are forms of the pure culture and not bacterial contamination. As to Vincent's case, the organism is distinctive and can not possibly be included in Wright's definition of *Actinomyces;* indeed, it forms one end of the *Streptothrix* group, while the *Actinomyces* of Wright forms the other.

SPECIES DETERMINATION.

Species determination in this genus is made extremely difficult, and classification of all the forms which have been given in the literature is impossible, because of the incomplete and imperfect descriptions which are given. Several of these descriptions are old, have not been repeated or confirmed, and are lacking in the elucidation of important points which are now recognized as essential for diagnosis. Our correspondence has elicited the fact that cultures of several of these species are no longer obtainable, and therefore, no further study of them can be made. Fortunately, we have been able to secure cultures of the most important members of the group and by comparative morphologic and biologic studies, particularly with reference to their pathogenic character, we have been able somewhat to simplify the classification by showing that some of the described species are identical. This includes *S. freeri,* which from a study of the literature we thought to be a new species, but after comparative study found to be identical with *S. eppingeri* in all essential particulars.

Another difficulty in establishing species or varieties is encountered in attempting to fix the amount of variation necessary to constitute a new species. The differences between various members of the group are practically in every instances those of degree only. For example; in the requirements for oxygen we have variations from facultative anaërobism with strong tendencies toward being negative to oxygen, as exemplified by the Wolf, Israel and Wright type of *Actinomyces,* to facultative aërobism with strong oxygen requirements, as exemplified in *S. eppingeri;* while other strains show intermediate stages of aërobiosis. Although strict anaërobes and equally strict aërobes have been mentioned, the conclusions probably are based upon errors in technique. Certainly this is true with the organisms with which we have worked, for in no instance have we encountered either a strict anaërobic, or an equally strict aërobic *Streptothrix,* although some of the cultures under our hands have had such properties ascribed to them by others.

Staining reactions.—The terminal filaments in lesions and young cultures usually stain very well by the usual aniline dyes, but in older colonies the central detritus does not stain and the filaments give irregular staining reactions often showing irregular, including coccus- and bacillus-like, forms. The reaction to Gram's solution is somewhat variable, depending upon the age of the colonies and there is some variation between the different species or varieties. However, in general, all strains are Gram positive to a greater or less degree.

Differences in *acid fast* properties have been used as being diagnostic in a number of described species, while unfortunately in others they have not been mentioned. These are important points in differentiation, but unfortunately such properties are a somewhat variable manifestation, depending in part upon the age and environment of the parasite and perhaps also upon other conditions, the nature of which is not clear. As with the oxygen requirements, degrees from the marked acid fast properties of *S. eppingeri* through those organisms showing the tendency only in certain portions, to *S. maduræ* which has no such properties are noted. *S. eppingeri*, often when taken from animal lesions and sometimes for example in cultures, will show acid fast properties which involve the entire organism, while in other cultures only portions of the organism will retain the fuchsin when decolorized and counter stained with Gabbet's stain.

Pigment production under certain circumstances is a property of most of the organisms of this group, as the cause of this is unknown and the result is variable, its diagnostic importance is lessened. Under like conditions, the color and general appearance of the pigment in any of these straine is usually fairly constant, but sometimes, particularly in animal tissues, it may show a more intense color. For example, *S. maduræ*, which usually produces a reddish-pink pigment in cultures, may, when inoculated into monkeys, at one time give a similarly colored pigment or again one considerable darker; so dark in fact as to appear almost black to the naked eye. The pigment of *Actinomyces* in our cultures shows but little color other than black. On media the color develops slowly and gradually to a dark gray, almost black. Some of the phenomena of pigment production and color may be explained, but in general the process is still obscure. For example, a darker pigment usually results in animals from the inoculation of fresh material from another animal than is the case if cultures are used. The next lighter shade is produced by inoculation with old, pigmented cultures, but color production is slower when young, unpigmented cultures are used for inoculation. Early pathologic lesions due to these parasites, like young cultures, rarely show pigment. The later in both instances is produced and grows more marked with age. Concentration undoubtedly has something to do with the apparent color of the pigment, for the harder the granule the darker the pigment appears to be.

Granule formation both in tissues and to a less extent, in cultures, is a property of all the pathogenic *Streptothricæ* with which we have worked. These granules vary considerably in consistency and color in the several species, but in the majority of instances they are made up of branching filaments with transformation products, which consist in irregular forms, crystals and unstainable detritus. The arrangement of the peripheral filaments may or may not be radial and there are various degrees of density of the mass. In two of our cultures (*S. canis* and *S. caprae*) there is less tendency to suppuration after inoculation in animals and the individual colonies have more the appearance of tubercles than in our other cultures. This difference has been pointed out by other observers. However, the lesions in our experimental animals were small; in the older lesions the type of the granule is not known, if we except the knowledge gained from the statements of the authors who described the parasites, the description being taken from the original lesions. The granules or colonies produced by the other cultures were in the majority of cases free in the necrosed, liguefied substance found in the various channels produced by these infections.

Club formation, in the lesions, in tissues and less frequently in cultures, is used as one of the points of differentiation between species of the organisms of this group. No doubt there is considerable variation in this respect under certain conditions, but the circumstances reported as surrounding club development are sufficiently varied and confusing to detract somewhat from what would otherwise be valuable for purposes of distinction.

Wright found club formation to be rather constant in original lesions, and observed it occasionally in certain cultures. In experimental lesions, it was also fairly constant, except in early lesions where clubs were sometimes absent.

Bostroem and others, working with species differing somewhat from Wright's organism in other particulars, also observed clubs both in lesions in animals and occasionally in cultures.

None of our cultures show definite clubs in culture or in experimental lesions in animals, although in several the terminal branches show some enlargement suggesting club formation (see illustrations). Our experimental animals were all killed within a shorter time after inoculation than were those of Wright, in which clubs were found.

Branching is similar in all of our cultures and is also similar to that recorded by most observers who have worked with this group of micro-örganisms.

The cultural characteristics of all of our strains have already been described. While there are variations in the reactions between some of these strains, they all appear to belong to one group of organisms, and if we analyze the literature carefully others, including the organisms of Wright and of Bostroem, may also be included in the group.

The following may be noticed if we take up the principal cultural characteristics comparatively as well as somewhat more in detail.

Surface growth is considered to be poor in Wright's organism and is not very profuse in some of our strains, but in Bostroem's organism and in most of ours, while it may be slow, it does occur in a satisfactory manner and in some strains it may be luxuriant. There is but little tendency for surface growth to spread in any of the cultures, but on the other hand, it heaps up, as it were, giving raised colonies sometimes 1 centimeter above the surface of the media. (See plates.) This is also true with Wright's organism, where surface growth appears.

Wright first called particular attention to the character of growth in glucose-agar suspension cultures. In this medium with his organism, there is a narrow zone 5 to 10 millimeters below the surface where the colonies are very numerous but small, while lower down they are less numerous, but of larger growth. Surface growth is the rule in our cultures in this medium, and only occassionally a colony may develop in its depth.

Stab cultures in sugar-agar.—Growth with Wright's organism occurred in small nodules along the course of the needle, it did not penetrate the medium to any extent and did not grow on or near its surface.

The growth in our cultures occurs mainly upon the surface and upper portion of the track of the needle.

Anaërobiosis.—Wright considers his organism as an obligate anaërobe, a statement which is somewhat qualified in the details of his work. For example, in discussing the growth upon glucose-agar suspension media he states that the most profuse growth of the organism is in a narrow zone 5 to 10 millimeters below the surface of the medium and that this way may be "explained as the result of a stimulating action exerted upon the growth of the microörganisms by the presence of a small amount of oxygen which has penetrated into the medium from the surface." This oxygen requirement is further illustrated by the author when he states that "in sugar-agar suspension cultures, placed under anaërobic conditions, there is little or no tendency to form colonies on the surface."

Growth occurred along the course of the needle only in stab cultures on glucose-agar. It did not penetrate the medium and, on the other hand, did not grow on the surface. However, when discussing growth upon surface inoculations in slanted solid media, Wright found that surface growth was not luxuriant and in some of his strains no growth occurred even under anaërobic conditions. Again, Wright observed that "in general, growth appears to be as luxuriant in bouillon either under aërobic or anaërobic conditions." To judge from the above and other statements which might be taken from Wright's excellent monograph and *according to the standards used in this report* for the other members of the group, Wright's organism must be considered to be a facultative anaërobe.

In *bouillon* media there is some variation between the manner of growth of our cultures, but little which may be considered of value in the differentiation of species. The tendency in some of our cultures is toward a surface growth which may gradually separate and fall to the bottom, or settle on the sides of the tube. In other instances, the majority or all of the growth may occur at the bottom of the tube. The medium is not clouded, but in some cases it becomes darker, apparently because of the absorption of pigment from the organisms. There are no essential differences between our cultures in bouillon and those reported by Wright.

Potato, as is well recognized, is not a very satisfactory medium for comparative studies, excepting where the same set of media is used. Fairly luxuriant growth was obtained in every instance with our cultures on potato slants.[2]

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[2] The potato slants employed in this laboratory are made from selected potatoes treated and prepared according to the rules laid down by the committee of the American Public Health Association.

There was not much variation between the different cultures except in the color of the pigment and the appearances which have already been described. Potato proved itself to be a very unsatisfactory medium for Wright's organism. Most of his strains grow on it very poorly, and some of them not at all.

Litmus-milk is not a favorable medium for the differentiation of species. Growth takes place slowly, and with two strains the color is slowly discharged. No other appreciable changes occur in the medium excepting with cultures of "chalcea," in which a slightly acid reaction is produced.

The favorable influence of *sugar* and *glycerine* upon cultures of all strains of the group of organisms has been noted repeatedly. Sugar or glycerine containing media not only are the best in securing growth, but with all our species pigment production is more active in these media.

Pathogenic characters.—The pathogenic character of many varieties of this group of organisms in the human and animal economy is well established. However, experimental inoculations in animals have not given constant results in the hands of other investigators, and our experiments have been uncertain with all animals except monkeys. The details have already been described and it only remains to state here that lesions similar in their gross and histologic appearances to the original ones produced by these organisms, have resulted with each of the strains which we have studied, except with one of the strains of *S. Madurae* which has already been mentioned in this discussion.

CONCLUSIONS.

There is, in human pathology, a very important group of branching, filamentous microörganisms which logically belong to a single genus. The generic name is variously given as *Streptothrix, Actinomyces* or *Nocardia;* the last of these names is probably scientifically the most correct, but because of the present botanical confusion and uncertainty the first is here employed, because of its more general acceptance.

The following species to judge from our work and from a study of the literature are the most important and may be recognized as established. There are probably a number of others but the description of many of them are too imperfect to allow of their recognition.

S. actinomyces Bostroem, 1890.
S. actinomyces Wolff & Israel, 1891 and Wright, 1905.
S. nocardii.
S. eppingeri.
S. maduræ Vincent.
S. capræ Silberschmidt.

The disease caused by infection with these parasites is properly named streptothricosis, with actinomycosis and nocardiosis as synonyms. Other names, such as lumpy-jaw, madura foot, mycetoma, etc., should be considered more as describing anatomic location rather than as designations relating to any special or specific cause of infection. Mycetoma might well be taken as the correct name for the group of infections if a strict interpretation of rules of nomenclature is followed, but usage renders it perhaps more desirable to retain the name as representing

Streptothricosis pedis. If mycetoma is to be considered in any more comprehensive light than this, it should become another synonym for streptothricosis. It should not be considered a disease caused by organisms other than *Streptothricæ.*

PART II.

STREPTOTHRICOSIS.

SYNONYMS.—Actinomycosis, Nocardiosis.

DEFINITION.—An infectious disease of man and animals caused by one or more species of *Streptothrix.* It is characterized anatomically by a peculiar, low grade of inflammation, usually confined to one part of the body, but in rare instances assuming the proportions of a general infection. The inflammatory process usually is accompanied by suppuration of a certain kind; the discharges contain granules made up principally of colonies of *Streptothrix.* The general picture of chronic inflammatory disturbance is seen clinically, and enlargement, suppuration and the presence of the causative organism in the lesions is observed locally.

HISTORY.—The history of *Streptothrix* infection is shown in the review of the literature given in Part I. In general it may be stated that the disease has probably long been recognized and frequent references are made in older medical literature to conditions which presumably were due to infection with these microörganisms. According to Rivolta, Trutto discussed the condition among cattle in Italy in 1785 under the name of "Krotenkrankheit." The colonies of the organisms were more or less accurately described by Langenbeck (1845), Sir T. Smith (1855), Lebert (1848), Rivolta (1868), Robin (1871), Heller (1872), Perroncito (1875), and others (see Ackland). Mention of the anatomical form of the disease generally described as mycetoma or Madura foot are also quite old, the principal authors being: Kämpfer (1712), Heynes (1806), Brett (1840), Gill (1842), Godfrey (1844), Colebrook (1844), Gunther (1844), Eyre (1848), Bollingol (1855), Eyre (1860), Collos (1861), Bidie (1862), Hirsch (1868 and 1886), Coquerel (1866), and many others (see *This Journal, Sec. B.* (1907), **2,** 487). Of these observers Colebrook (1850), Bollingol (1855), Coquerel (1866), Maxon and Hogg (1870), Bristowe (1871), Berkeley (1876), and others probably saw and in a few instances partially described the organisms present in the lesions. However, the really important history of *Streptothrix* infections dates from Vandyke Carter's work (1859–1874). This author described and illustrated the parasites in many cases of the foot (Madura foot) type of the infection. Bollinger and Marz (1876) first accurately described and named one of the parasites causing the disease known as lumpy-jaw in cattle. The next epoch in the history was due to an article by J. Israel (1878) who was the first to describe the disease and parasite in man in locations other than the foot (Madura foot) and hand, the infection in these places already having been described by Carter and others. Israel's work was followed by that of Ponfick (1879) with strong evidence as to the identity of the disease in man and animals. From the year 1876 the literature accumulated rapidly and the infection was reported for man and animals from widely varying locations and countries.

Bostroem (1890) contributed the first thorough and exhaustive laboratory study of the microörganisms and this work was followed a year later by an equally exhaustive treatise on the same subject by Wolf and Israel. The organisms described by Bostroem on the one hand and by Wolf and Israel on the other, although isolated from apparently similar diseases, showed certain morphologic and biologic differences which led to much discussion during the next few years. Organisms corresponding to the descriptions of both these pioneer observers continued to be mentioned in the literature, each investigator maintaining his organism to be the true cause of the disease.

In 1888 Nocard cultivated and quite accurately described a *Streptothrix* as the cause of a disease locally termed *farcin de boeuf* of cattle in Guadalupe; Nocard's organism seemed to be of a different species from either Bostroem's or Wolf and Israel's. Eppinger (1890) cultivated and accurately described another species of *Streptothrix* as the cause of a brain abscess and "psuedotuberculosis" in a man. Vincent (1894) first satisfactorily cultivated and described a *Streptothrix* as the cause of mycetoma or Madura foot and his organism seemed to have certain characteristics showing it to be specifically different from any of those previously described.

Foulerton (1899–1907) gave descriptions of several new species of the parasites and has brought out the most thorough and exhaustive consideration of the whole subject with which we are familiar. Wright (1905) contributed a most complete and exhaustive study of the biology of the Wolf and Israel variety of this organism. The work of bringing all this group of similar organisms together in a single genus is largely due to the researches of Rossi Doria, Petruschky, Foulerton and several other recent writers, particularly of the German and French observers.

In this article we have shown conclusively that Eppinger's organism isolated from clinical actinomyces on several occasions is identical with *S. freeri*, which is one cause of Madura foot in the Philippine Islands. Very little is known regarding *Streptothrix* infections in this Archipelago. Our records show two cases in which *Actinomyces* was the etiologic factor in human disease, and several infections of cattle have been observed in the islands. One case of the Madura foot type of the disease has been seen.

ETIOLOGY.—*Predisposing causes*, for this disease, except in a few instances, have not been sufficiently studied to make a satisfactory estimate of their influence.

The *geographic distribution* is very wide, but no very large series of cases have been studied by any one observer. Collections of such series have been made in America, Germany, France, England, Russia, Switzerland, and in the British colonial possessions. The most frequent incidence is found in certain parts of the Tropics, particularly in India, but, as has been pointed out by Ackland, the disease may be overlooked in a community for a long time until special attention is called to its prevalence.

According to available statistics the infection is more frequent during young, adult life, but cases have been reported in children and in old people. Males are much more frequently affected than females—295 males to 110 females being given in Leith's statistics, and 65 males to 36 females in Ackland's.

Race, nationality, residence, overcrowding, climate, occupation, and physical condition, to judge from available statistics, seem to exert but a minor influence on the spread of the disease, although a more careful study of a large material may show some of these to have greater significance.

General environment and *mode of living* would naturally be expected to have considerable influence as predisposing factors, particularly in determining the part of the body involved. For example, the Madura foot type of infection is most common among people who go barefoot, it being largely a wound infection.

Streptothricæ are the specific, causative agents of the infection. They have already been considered in Part I of this report, and only a brief summary will here be given.

SYNONYMS.—*Actinomyces, Nocardia, Oöspona, Chenaphe carteri.*

DIAGNOSIS of these organisms is made from morphologic and biologic considerations. They are branching, filamentous organisms, which develop slowly into colonies made up of the branches and their "transformation products." These colonies vary in color, size and consistency, and when stained show various changes in different portions. The filaments at the periphery are usually intact, with or without club formation, and the terminals may or may not be radially placed. Toward the center of the colony, or granule, irregular forms, such as coccus- and bacillus-like ones, are found, together with crystals and nonstaining detritus.

The majority of these organisms may be cultivated on artificial media, where they show various but characteristic biologic properties. That some of them are pathogenic tissue parasites is shown by their action on laboratory animals.

Morphologically these parasites are rather closely related to some of the branching bacteria. The young filaments vary in width from 0.5 to 1 μ and in length from 5 to 20 μ or more. They usually stain homogeneously, and in some strains taken from lesions they are acid-fast to the

Ziehl-Neelsen-Gabbett method. In older forms the segments are often broken, the sheath-like substance not showing either in fresh or stained specimens. The breaking up of the filaments produces great variety and size of irregular forms; some of these may appear to be very much like bacteria, but their true nature is easily established by laboratory methods. The majority of these organisms may be stained by the aniline dyes, all show Gram positive characteristics to a greater or less degree, and several are as acid-fast as is the tubercle bacillus.

Biologically certain species—both saprophytic and pathogenic—are widely distributed in nature. They have been found on food stuffs—particularly cereals—in water, air, soil, etc. Zoölogically they are found in some insects and several animals, and in man. Cattle are the most frequently infected of the animals, but rarer instances of the disease have been reported for other species.

Cultivation of these organisms is probably possible with all species, although several authors have reported failures, and all observers have noted the difficulty of obtaining a culture from the lesions in animals. However, when adaptability to artificial media has once been secured, no very great difficulty is found in keeping the culture. In general, it may be stated that these organisms grow slowly on artificial media, but that the cultures show most positive characteristics in the majority of instances. In all there is a tendency to "pile up" on the medium rather than spread over the surface. Pigment production of various shades is a very common property, and this is more marked as a rule in glycerine or glucose containing media.

Resistance to physical, chemical, and other agents by these organisms is rather great if we consider them to be non-spore bearing parasites, but this resistance is not sufficient to permit us to consider that true spore formation is present as it is understood for bacteria.

PATHOGENIC CHARACTER.—The pathogenicity of several species of *Streptothrix* has recently been demonstrated by different workers, according to the accepted bacteriologic rules governing such decisions. Other members of the group appear to be saprophytes in that they do not produce lesions in animals by the usual methods of procedure. There is also considerable lack of uniformity in the results of animal experiments with nearly all the pathogenic strains. However, working with monkeys, our results have been more uniformly successful than those reported by other observers, or than our own results with other laboratory animals. The pathogenicity of this group of organisms seems to be influenced to a certain extent by the same conditions which produce changes in the virulence of bacteria. Not only may the virulence of some of these species be increased by passage through susceptible animals, but with the increased virulence differences in cultural results may be noticed. These are shown principally in greater difficulty in securing growth, in a slower growth on artificial media and sometimes in slight changes in the color and quantity of pigment production.

Some of the so-called saprophytic species may in reality be found to be pathogenic, when improved technique is used.

Modes of transmission.—Although experimental evidence is still far from satisfactory regarding modes of transmission, it seems to be entirely reasonable to assume from the known biology and the available evidence, that transmission may take place both directly and indirectly. So far as we are aware, no positive examples of direct transmission from person to person have been reported, but that such infection does not take place in localities with high incidence of the disease, seems probable. Rather convincing evidence of indirect transmission through the agency of food-stuffs, water, etc., has been furnished by several observers. Several authors whose work has already been reviewed, have shown that pathogenic species may be isolated from water, air, soil, and food-stuffs and the history of many of the reported cases indicates infection from some such source. The frequent presence of the infection in the lower animals must not be forgotten in considering the manner of transmission of the parasites.

Infection probably takes place in two general ways, first, by direct or wound infection, as is shown in many cases by the history of injury before the development of the symptoms of the *external* forms; and secondly, infection by way of the respiratory or gastro-intestinal tracts, which is shown in many of the *internal* forms of the disease.

Species.—The number of species important in this disease is probably a considerable one. Those which we have been able to recognize from the literature and our own work are given in Part I.

It seems probable that all the species have not, as yet, been discovered and that some, which have been described, are specifically different from the ones mentioned here.

PATHOLOGY.—In general the morbid changes found in this disease are those of a peculiar, low-grade, chronic infective process. Anæmia, atrophy of tissues, and mild, chronic degenerations of parenchymatous organs are present. The special pathology depends somewhat on the part of the body involved and on the extent of this involvement. The streptothritic unit, as it were, is a granule which is usually surrounded by a zone of peculiarly appearing suppuration, and this in turn by an area of inflammation characterized by connective tissue proliferation and cell infiltration. Cells of the usual character are found, with a relative increase of fixed tissue cells and occasionally a giant cell. In other instances the suppurative zone is absent and the streptothritic unit takes on more the general and histologic appearance of a tubercle. In fact, the whole morbid process of *Streptothrix* infections resembles more or less closely that produced by *Bacillus tuberculosis*. Tissue destruction often spreads by means of continuity, but more usually by intercommunicating channels running in various directions. These channels contain the broken down tissue and granules made up of colonies of the infecting organism. Few tissues escape the destructiveness of the *Streptothrix,* but it appears to be more active in the connective tissues, bones, and mucous membranes. However, practically every organ and tissue of the body has been involved. The disease spreads through the body in at least two ways, by directly continuing along the tissues, in which case the area involved is rarely great, and by metastases through the blood vessels, when the infection may be so great as fairly to be considered a general infection.

The character of the morbid process suggests that the minute action is toxic in character, although if such is the case, the toxin must act very slowly. The lymphatics near a diseased process may be enlarged, but are rarely found to be broken town or to contain the microörganism.

SYMPTOMS.—The clinical manifestations of *Streptothrix* infections are essentially those of a slowly developing, chronic inflammatory process. They vary much with the location of the lesions and further complications are secured by the presence of mixed infections which are frequent when the disease attacks regions of the body exposed to bacterial invasion. In many instances, where the lesions are located in the internal organs such as the liver, definite clinical manifestations do not occur and unless the infection spreads, its nature in all likelihood is not recognized during life.

When the lesions are located externally, or in places where the discharges reach the surface of the body, the nature of the infection should be suspected from the appearance of the wound and the character of the discharges; on the other hand, it may be generalized, manifest itself in an acute course and be difficult to distinguish from a pyæmia of other etiology.

The *incubation* period varies between wide limits, and as given by authors may be from a few days to more than two years. The onset is usually gradual, by the slow development of the lesions.

The following clinical varieties may be recognized:

Generalized streptothricosis.—This form of infection has been noted by several observers. It occurred 9 times in Ackland's 109 cases. This type usually begins in a local lesion and is transmitted through the blood vessels. In the majority of instances, it occurs in mixed infections with bacteria, but cases in which no bacteria were present have also been reported. Several species of the organisms causing these general infections have been found. This type is generally acute or subacute clinically and the symptoms as given by various authors are similar to septicæmia or pyæmia from other causes. Extensive lesions may occur in practically every organ and tissue of the body. The diagnosis is only made by laboratory methods, the prognosis is bad and treatment unsatisfactory.

Thoracic streptothricosis.—The organs of the chest, particularly the lungs and pleuræ are most frequently involved in this disease. It occurred 65 times in 257 cases reported by Duvan and 29 times in Ackland's 109 cases. The clinical symptoms in the lungs and the physical signs may resemble a chronic tuberculosis or severe bronchitis and the pleural involvement may consist of chronic, adhesive pleuritis or more often of empyæma. Unless there is perforation of the chest wall or metastases, the clinical manifestations in these types show nothing characteristic of the disease and the true nature of the infection can only be determined by laboratory methods. Streptothricosis of the heart and mediastinum have been reported, and Ackland notes nine cases involving the œsophagus.

Abdominal streptothricosis, including all the organs of the abdominal and pelvic cavities, have been reported by various observers. The liver and gall bladder suffer most often. Involvement of these viscera occurred forty times in Duvan's series and thirty-three in Ackland's. The appendix is quite frequently involved and in some instances is the primary seat of the lesions.

Other lesions are found in the mesentery, intestine, rectum, spleen, bladder, prostate, testicle, kidneys, and abdominal wall. In none of these types are there any characteristic clinical manifestations which differentiate this infection from other chronic inflammatory conditions of tuberculous or other etiology in the same locations.

Cerebral streptothricosis includes involvement of the brain, cord, meninges, and nerves, as well as the other tissues in these organs. The central nervous system was involved 19 times in Duvan's 257 and 5 in Ackland's 109 cases. Several different species of the organisms have been found in these lesions, that of Eppinger being the principal one. This species, as has been shown in Part I of this report, is identical with *S. freeri* which caused the mycetoma in our case. The reported cases show no characteristic symptoms in these types of infection.

External streptothricosis may involve any of the external or contiguous tissues, including the mouth and jaw, neck, skin, and subcutaneous tissues, conjunctiva, nose, and extremities. "Lumpy-jaw" or "big-jaw" is one of the most frequent of these various types; mycetoma, Madura foot or *streptothricosis* pedis is a very common tropical type and others involving many anatomical locations are frequently encountered. Practically all described species of the genus of the organism have been found at one time or another in external streptothricosis, and there does not appear to be much variation in the clinical picture because of any special species or variety. The clinical manifestations of external streptothricosis are rather characteristic. The peculiar, crater-like skin lesions of a chronic character leading through ramifying channels, through which is discharged the peculiar, oily, pus-like substance containing granules, makes a rather constant and characteristic picture. As we have already stated, mycetoma or Madura foot is best classified here as the clinical type of *Streptothricosis pedis,* because it may be caused by several if not any of the species of this genus and the clinical manifestations are practically the same in all cases. The special symptoms of this type are well known and have already been discussed in this report.

Miscellaneous types of streptothricosis may be mentioned, such as involvement of the conjunctiva, bones, ear, nose, intercostal spaces, etc. Their only peculiarities are in the anatomical locations of the lesions.

DIAGNOSIS.—The diagnosis of *Streptothrix* infections is made clinically by the character of the exposed lesions and discharges and by laboratory methods. Obviously, the common and frequent involvement of internal organs is rarely recognized except by microscopic examinations at operations or at autopsy. The thoracic types may be determined by microscopic and bacteriologic studies of the sputum or aspirated fluid from the pleural cavities. It is generally stated by competent observers that these types are frequently overlooked, even in sputum examinations and it is not improbable because of the acid-fast properties of some of the organisms that they may occasionally be mistaken for the tubercle bacilli. The resemblance may, at times, be quite close. In some of our experimental lesions the similarity has been striking. The microscopic examination of material from exposed lesions often requires some patience and care to enable the observer to find the organisms; unless a granule is encountered, when, of course, the determination is easy. Inasmuch as some other closely related organisms such as *Oïdia, Leptothrix,* and *Cladothrix* may cause somewhat similar lesions, *Streptothricæ* should not be diagnosed positively without careful microscopic study of the organisms present in the lesions.

PROPHYLAXIS.—From what we know of the distribution of the organisms of this disease and the mode of transmission and the prevalence of certain anatomical types, prophylaxis should consist in guarding against wound infection and generally by care in food and drink. In the Tropics most of the types consist in local foot or other skin wound infections, which should be guarded against by wearing shoes and by promptly treating skin wounds and abrasions according to antiseptic methods.

PROGNOSIS.—The prognosis depends to a considerable extent upon the location and extent of the lesions. The general infections and those of the internal organs almost always end fatally. The external types are much more amenable to treatment and the mortality is small.

According to the statistics of Duvan, and Poncet and Berard who analyzed 257 cases, the mortality was as follows: Skin, 2.3 per cent; face and neck, 10; jaw and temporal region, 30; abdominal cavity and intestine, 65; thoracic, 85; liver, 100, and brain and spinal cord, 100 per cent. The mortality in mycetoma, under proper treatment, is very small. The course of the disease is usually chronic, but it may be general

	Streptothrix eppingeri from Foulerton "A."		Streptothrix eppingeri from Foulerton "B."		Streptothrix nocardi.		Streptothrix maduræ from Strong.	
	Literature.	Our culture.	Literature.	Our culture.	Literature.	Our culture.	Literature.	Our culture.
Morphology	Mycelium with branching threads ending in spores of an elongated appearance and also showing clubbed ends.	Various forms noticed, depending upon the age of the culture and media, from small oval to long branching filaments. The diameter is fairly constant. No sheath observed and no clubs.	Foulerton has not yet published the details regarding this organism.	Similar to Eppinger's original culture.	Long, thin, hyphæ twisted in masses showing many branching forms.	Many coccoid forms; short plump filaments with short branching hyphæ occur, in young cultures; in older cultures ovoid forms predominate.	This oganism has not previously been described.	Long, thin, filaments with true branching; no club forms.
Staining characteristics.	Cultures from 2 to 3 months old stained by Ziehl-Neelsen method show many portions which are acid-fast but not alcohol-fast.	Portions of filament acid-fast by Ziehl-Neelsen method; ovoid forms were decolorized; spore-like bodies and portions of mycelium are Gram-positive.		Similar to Eppinger's original.	Cultures from 9 days to 3 months old stained by Ziehl-Neelsen method show many acid-fast portions; these are also alcohol-fast.	Cultures stained by Ziehl-Neelsen method show many acid-fast portions. The organism is Gram-positive.		Cultures stained by Ziehl-Neelsen method showed no acid-fast portions. Gram-positive with irregular staining.
Growth on ordinary agar.	Small whitish colonies which coalesce into a thick adherent membrane with elevations and depressions of an orange color.	Growth appears after 2 days as smooth, adherent membrane at first a porcelain-white, later a delicate orange color; medium remains moist.		do.	Small, white, irregular, round, opaque colonies which form an adherent, thick, wrinkled membrane-like lichen.	Small, white, irregular, round, opaque colonies; growth slow and not abundant on this medium; no pigment.		Grows very slowly and very little pigment is produced.
Glycerine-agar.		Growth appears after 3 to 4 days, at first as small whitish colonies which gradually take on a delicate pink color. Later as the colonies develop they become umbilicated and coalesce forming a heaped up growth and producing an orange color.		do.		Appears after 3 days as discrete colonies; later the colonies coalesce and become heaped up, presenting a moist, mealy growth. This organism does not produce pigment.		Growth appears after 5 days as small pinkish-white colonies; later the colonies develop a heaped up growth and assume a wrinkled appearance with a deep-pink color.
Maltose		Similar to glycerine-agar				Similar to glycerine-agar		Similar to glycerine-agar
Potato	Growth appears after 48 hours as a granular layer, at first white, becoming yellow to brick-red. This is later covered by a fine, white, powdery efflorescence, culture resembling a sugar almond.	Growth appears after 48 hours as a granular layer at first white, becoming yellow to brick-red.		Growth appears after 48 hours, similar to Eppinger's original.	Growth appears after 48 hours as a buff-yellow granular growth; no pigmentation or erosion of medium.	Growth appears after 48 hours as a buff-yellow granular growth.		Growth appears after 3 days as small, pinkish-white colonies; these later develop a dark pink, raised growth.
Boullion	Growth appears after 24 hours as a small, white granule, forming a pellicle and adhering to sides of tube; some portions fall to the bottom. No pigmentation of medium.	Similar to literature		Similar to Eppinger's original.	Growth appears after 24 hours as a grayish, flocculent mass at the bottom of the tube.	Growth appears after 24 hours as a grayish, flocculent mass at the bottom of the tube; later a few grayish granules appear on the surface and in some instances puffball formation occurs at the bottom of the medium.		Growth appears after 5 days as a coherent mass at the bottom of the tube; surface growth rare.
Ascitic fluid		After 6 days very slight growth occurs on the surface of the medium; no pigment; no clubs.		do.		Very slight growth at the bottom of the tube; no pigment; no clubs.		Very slight growth; no pigment
Pathogenicity for lower animals.	Not pathogenic for white mice. 3 rabbits inoculated subcutaneously recovered after developing temporary local swellings. 1 rabbit inoculated in anterior chamber of eye developed a nodule on the iris but no general infection. 1 rabbit inoculated intravenously and another in the kidney died on the fifth and seventh days respectively. Two guinea pigs inoculated intraperitoneally died on the eighteenth and twenty-fourth day.	Pathogenic for rabbits, guinea pigs and monkeys by intraperitoneal injection.		do.	Rabbits, dogs, cats, horses, and oxen are not affected by intraperitoneal or intravenous injections. In guinea pigs intraperitoneal or intravenous injections cause constantly within 20 days, a miliary tuberculosis similar to that produced by *Bacillus tuberculosis*.	Pathogenic for guinea pigs and monkeys by intraperitoneal injections.		Pathogenic for monkey by intraperitoneal injection.

Cultural characteristics of various types of Streptothrix and of Actinomyces.

Streptothrix maduræ from Vincent.		Streptothrix maduræ from Foulerton.		Streptothrix capræ Silberschmidt.		Streptothrix canis, our culture.
Literature.	Our culture.	Literature.	Our culture.	Literature.	Our culture.	
Many twisted filaments showing true branching forms; the mycelium shows a ray-like growth at the periphery but no true club forms; some of the hyphæ show an enlargement along their courses.	Long, thin filaments with true branching; no club forms. These hyphæ may or may not be radially placed at the periphery of the granule.	Similar to *Streptothrix maduræ* of Vincent.	Similar to *Streptothrix maduræ* of Vincent.	Twisted, branching filaments which break off at the end into forms resembling bacilli or cocci. A few of the shorter forms show clubbed ends.	Short filaments resembling bacilli and many coccoid forms; occasionally longer filaments showing branching but no club forms.	Short, plump, filaments; many resembling bacilli; oval and coccoid forms.
Culture 1 week old stained by Ziehl-Neelsen method showed no acid-fast portions.	Cultures stained by Ziehl-Neelsen method showed no acid-fast portions. Gram-positive with irregular staining.	do	do	Irregular staining.	Cultures from 2 weeks to 2 months old stained by Ziehl-Neelsen method show many acid-fast portions, giving the organism the appearance of short, plump bacilli. Gram-positive, irregular staining.	Culture stained by Ziehl-Neelsen method shows many acid-fast portions. The organism is Gram-positive in portions, giving it the appearance of cocci and short bacilli.
Small projecting, round, whitish-yellow colonies which slowly take on a rose color; they show umbilication in the center and become confluent and adherent to the medium.	Grow very slowly on this medium; after 4 days small, whitish-yellow colonies develop.	do	do	In 2 or 3 days varicose, shriveled, brownish-white colonies appear which form an adherent, brown, irregular membrane in from 8 to 15 days.	Growth appears in 2 or 3 days as small brownish colonies; medium remains moist; does not grow so well nor does it produce the pigment on this medium that it does on the sugar-containing media.	Grows as a smooth, glistening, brownish-white colony; does not grow so well on this medium as on sugar-containing media.
	Growth appears after 5 days as small, pinkish granules and later assumes a dark-pink color.		Similar to *Streptothrix maduræ* of Vincent with the exception that its pigment is a more delicate pink with a pale periphery.		Growth appears after 2 days as small, brownish-white colonies which later coalesce giving the growth a moist, mealy appearance with a light-brownish color.	Appears after 2 days as small brownish-white colonies. These later assume an ocher color. The colonies soon coalesce giving culture a moist, mealy appearance.
Growth appears after 8 days as small, discrete, yellowish-white colonies with waxy, wrinkled surface; later often developing pink pigment.	Similar to glycerine-agar.		Similar to glycerine-agar.		Similar to glycerine-agar.	Similar to glycerine-agar.
	Growth appears after 3 days as small, pinkish-white colonies, which later develop a dark pink, round, granular growth.	Growth appears after 72 hours as a heaped-up, irregular mass of a creamy-yellowish-white color, often showing patches of pink coloration; no pigmentation or erosion of medium.	Similar to *Streptothrix maduræ* of Vincent.	Colonies in 4 to 8 days which form a dry, brown, raised growth.	Appear after 3 days as slightly raised colonies which soon assume a light-brown color.	Growth appears after 2 to 4 days as slightly raised, white colonies; these later assume a light brown color.
Growth appears as opaque-white, granular, more or less cohering colonies at the bottom of the tube; surface growth rare; no pigmentation of medium.	Similar to literature.	Similar to *Streptothrix maduræ* of Vincent.	do	Colonies develop on surface as concave, fine, dry, pale disks which latter form a surface membrane; fluid clear but a deposit forms in the bottom of the tube.	Colonies develop on the surface as fine, dry disks and later form a surface membrane; a deposit forms at the bottom of the tube; medium remains clear.	Growth occurs as a thin, white membrane on the surface of the medium; a deposit forms but the medium remains clear.
	Very slight growth; no pigment.		Very slight growth; no pigment.		Very slight growth; no pigment.	Very slight growth; no pigment; no clubs.
The inoculation of cats, rabbits, guinea pigs, and mice produced nothing more than a small nodule at the site of injection and these disappeared (Vincent). Nocard carried out intraperitoneal, intravenous and subcutaneous inoculations of dogs, sheep, rabbits, guinea pigs, fowls and pigeons; his results were negative in every case.	Negative results in monkeys by intraperitoneal inoculation.	Similar to *Streptothrix maduræ* of Vincent.	Extensive lesions were produced by intraperitoneal injection in monkeys; lesions contain granules with organisms and are similar to those seen in madura foot.	Pathogenic for guinea pigs by subcutaneous and intraperitoneal injections.	Pathogenic for guinea pigs and monkeys by subcutaneous and intraperitoneal injections.	Intraperitoneal injections in monkeys produced numerous miliary tubercle-like bodies in the peritoneum and mesentery.

Streptothrix chalea Foulerton, our culture.	Actinomyces from Pasteur Institute.		Streptothrix freeri.	
	Literature.	Our culture.	Literature.	Our culture.
Long, thin, filaments with branching hyphæ.	Ray fungus consisting of a mass of mycelia, containing many spores in center; branching forms present.	Radiating mycelium containing many spore-like bodies in center; true branching occurs.	Similar to morphology described.	Long, branching filaments, 2 to 7 μ in diameter. Transverse segments are shown of various length from coccoid to 10 μ in length. Branching occurs as lateral hyphæ developing from the segments. The filaments have a definite wall. Spores have not been observed. Coccoid and club-like forms present in certain medium.
No acid-fast portions by Ziehl-Neelsen method of staining. Gram-positive for portions.	Culture stained by Ziehl-Neelsen method shows no acid-fast portions. This organism stains well by the Gram method.	Culture stained by Ziehl-Neelsen method shows no acid-fast portions. This organism stains well by the Gram method.	......	Culture from 5 days to 2 months stained by Ziehl-Neelsen method show many acid-fast portions. The organism is Gram-positive.
Grows as dark-brown, adherent membrane.	Small, opaque colonies which later show a white, downy appearance and which coalesce into an adherent, wrinkled, lichen-like membrane.	Small, opaque colonies which later become black and in time produces a bright yellow membrane; the medium becomes dark.	Similar to morphology described.	From 2 to 3 days' growth appears as smooth, glistening colonies which later coalesce and produce a delicate pink pigment; medium remains moist.
Grows as a dark-brown, adhering membrane.	......	Small, opaque colonies which later coalesce, developing a tough, black membrane; as growth proceeds a bright yellow pigment is produced on the surface of the membrane; the medium also takes on a dark color.	......	Growth after 3 to 4 days at first as small, whitish colonies; these gradually take on a delicate pink color; later as the colonies develop they become umbilicated and coalesce forming a heaped-up growth and produce a burnt-ocher color.
Similar to glycerine-agar.	......	Similar to glycerine-agar......	......	Similar to glycerine-agar.
Grows as a dark-brown, adhering membrane.	......	Similar to glycerine-agar; medium becomes moist.	......	Do.
Growth from the planted material in the bottom of the tube; no surface growth.	Opaque, granular, like grape seeds, which coalesce to a loose, flaky sediment; no surface membrane forms.	Growth occurs in the bottom of the tube as a film containing many black granules; no growth on the surface of the medium.	......	Growth appears after 3 days as flat particles on the surface of the medium; these produce in time a delicate pink color; as growth proceeds a granular mass collects in the bottom of the tube; this mass is more or less coherent.
Very slight growth; no pigment; no clubs.	......	Very slight growth; no pigment; no clubs.	......	Very slight growth; no pigment; no clubs.
Negative	......	Intraperitoneal injection in monkeys produces extensive suppurative lesions containing many small, black granules.	......	Pathogenic for guinea pigs and monkeys by intraperitoneal injections.

and acute and general infection may take place during the course of a chronic localized type of the infection.

Complications.—While streptothricosis may be found together with a number of other diseases, or may develop its symptoms as sequelæ of other diseases, the principal direct complications are those due to mixed infections of bacteria. Several of the pathogenic bacteria have been found associated with *Streptothricæ* in lesions and the course and outcome of the disease is influenced accordingly.

Tuberculosis, because of its close clinical relation to streptothricosis and the frequent lung involvement of both organisms, has led to confusion in some of the reported cases.

Treatment.—The varieties of treatment most useful in this disease are general, as well as local surgical intervention if cause is indicated and a combination of all of these methods may be necessary. Potassium iodide administered in large doses over a long period of time is generally admitted to have a favorable influence on the course of the disease and complete cures have been reported from this method of treatment. Local measures consist in antiseptic dressings and the use of the Roentgen rays. Surgical measures consist in drainage, removal, or amputation according to the location and extent of the lesions. A combination of all three forms of treatment would suggest itself as offering the most favorable opportunity for recovery.

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ILLUSTRATIONS.

(Colored photographs and photomicrographs are by Charles Martin, photographer, Bureau of Science, Manila.

PLATE I.

FIG. 1. Cultures of *S. eppingeri* from Foulerton's case.
2. Culture of *S. eppingeri* from original strain.

PLATE II.

FIG. 3. Culture of *S. maduræ* from Foulerton.
4. Culture of *S. maduræ* from Strong's culture.

PLATE III.

FIG. 5. Culture of *S. maduræ* from Vincent's strain.
6. Culture of *S. actinomyces* from Binot.

PLATE IV.

FIG. 7. Culture of *S. nocardii.*
8. Culture of S. *capræ.*

PLATE V.

FIG. 9. Culture of *S. canis.*
10. Culture of *S. freeri.*

PLATE VI.

FIG. 11. Culture of *S. freeri,* showing structure of individual colony.
12. Culture of *S. chalcea.*

PLATE VII.

FIG. 13. Section from experimental lesion in monkey produced by inoculation with culture of *S. eppingeri*, × 60.
14. Unstained smear preparation from culture of *S. eppingeri*, × 600.
15. Smear preparation from culture of *S. eppingeri* stained by gentian violet, × 800.
16. Section from experimental lesion in mesentery of monkey produced by inoculation with culture of *S. eppingeri,* × 600.

PLATE VIII.

FIG. 17. Smear preparation from culture of *S. maduræ* stained by gentian violet, × 400.
18. Same as No. 17, × 600.
19. Section from experimental lesion in monkey produced by inoculation with culture of *S. maduræ,* × 60.
20. Smear preparation from culture of *S. canis* stained by gentian violet, × 650.
21. Same as No. 20, × 650.

PLATE IX.

FIG. 22. Smear preparation from culture of *S. maduræ* (Strong's culture) stained by gentian violet, × 500.

23. Same as No. 22, × 700.

24. Same as No. 22 excepting that the preparation is unstained, × 500.

25. Smear preparation from culture of *S. actinomyces* (Pasteur Institute) stained by gentian violet, × 700.

26. Section from experimental lesion in monkey produced by inoculation with culture of *S. maduræ*.

PLATE X.

FIG. 27. Smear preparation from culture of *S. capræ* unstained, × 600.

28. Section from experimental lesion in monkey produced by inoculation with culture of *S. actinomyces*, × 600.

29. Smear preparation from culture of *S. actinomyces* stained by gentian violet, × 650.

30. Smear preparation from unstained specimen of *S. actinomyces*, × 650.

PLATE XI.

FIG. 31. Smear preparation from culture of *S. capræ* stained by gentian violet, × 650.

32. Section from experimental lesion from monkey produced by inoculation with culture of *S. capræ*, × 600.

33. Smear preparation from culture of *S. capræ* stained by gentian violet, × 1100.

34. Section from experimenal lesion in monkey produced by inoculation with culture of *S. capræ*, × 60.

PLATE XII.

FIG. 35. Smear preparation from culture of *S. chalcea* stained by gentian violet, × 850.

36. Smear prepration from cultures of *S. nocardii* stained by gentian violet, × 850.

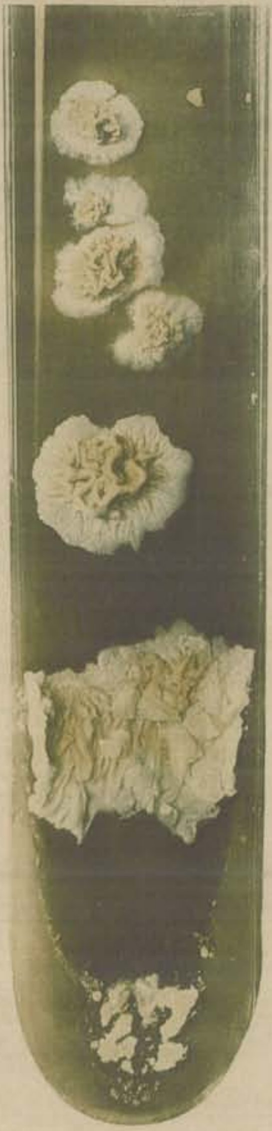


Fig. 2.

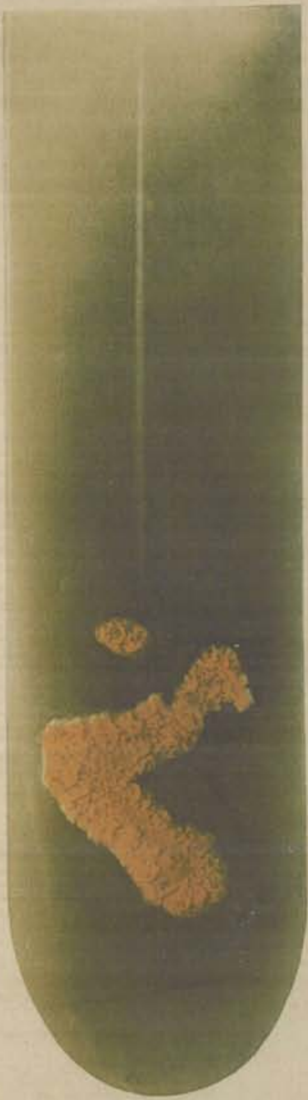
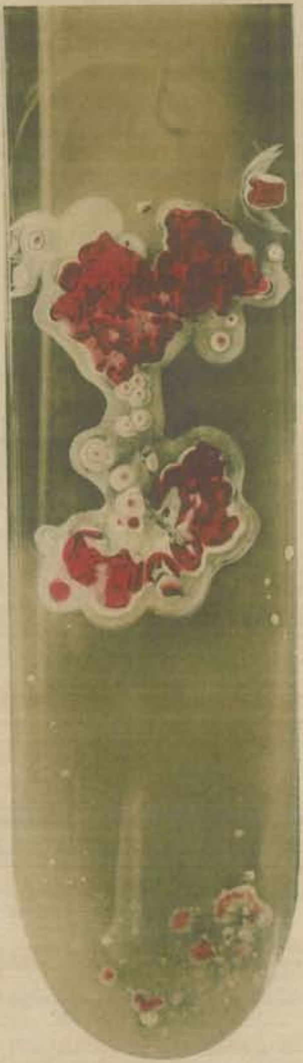


Fig. 1.

PLATE I.



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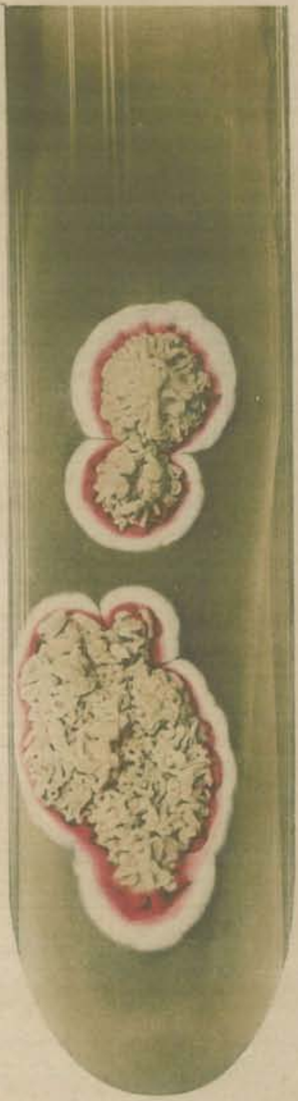
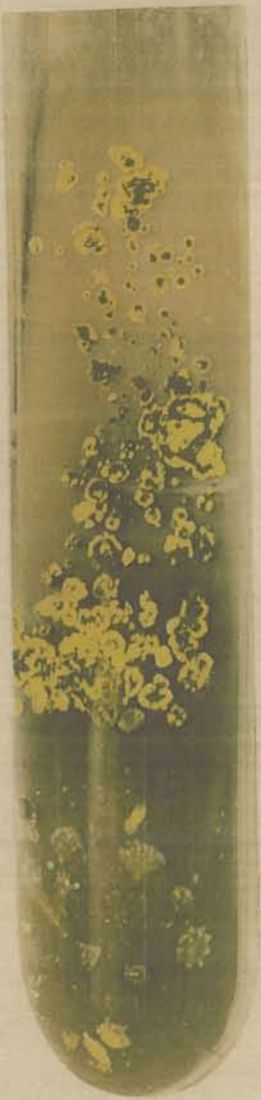


Fig. 3.

PLATE II.



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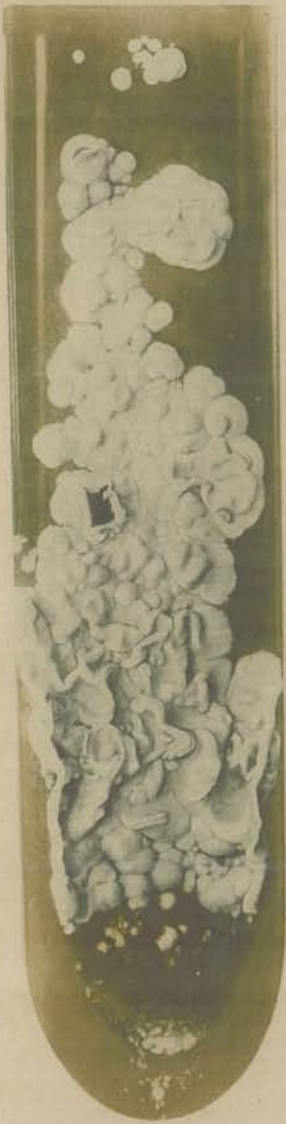

Fig. 5.

PLATE III.

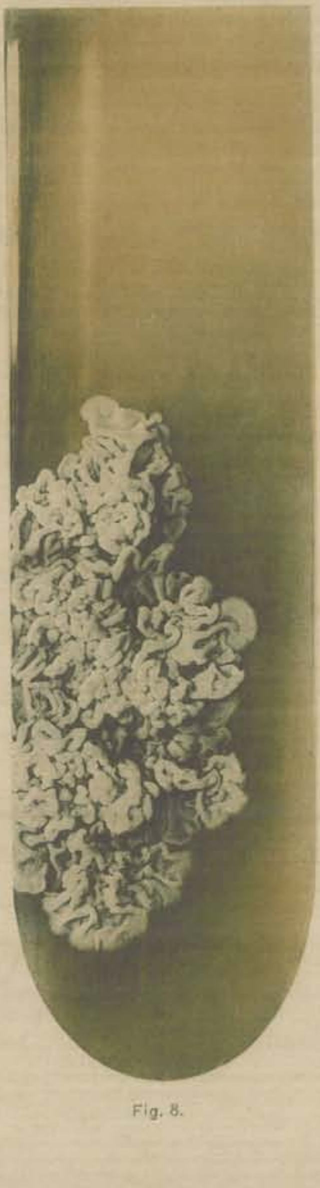

Fig. 8.

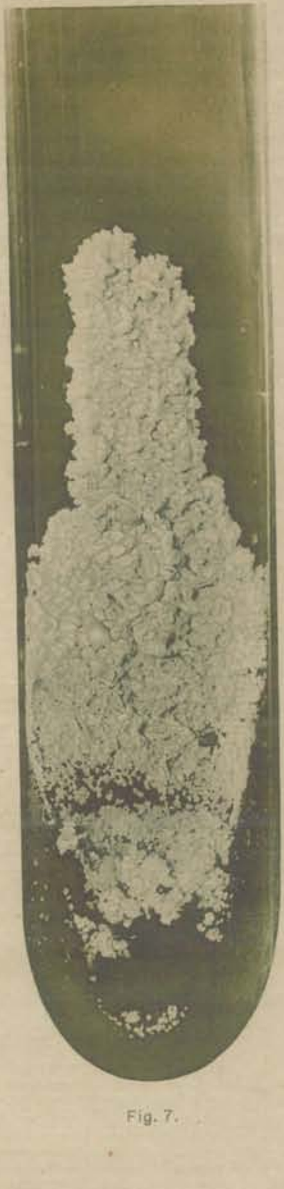

Fig. 7.

PLATE IV.

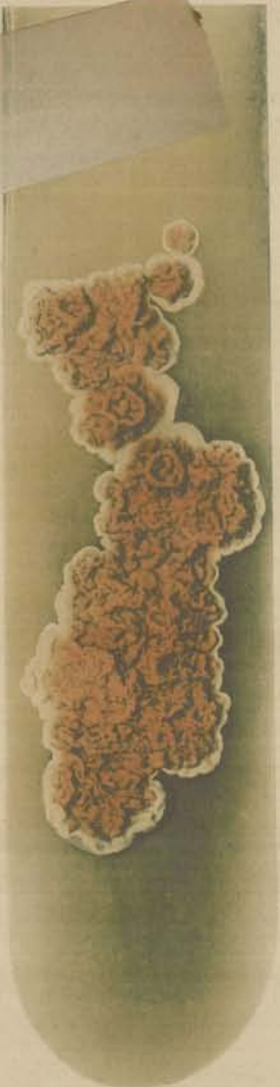

Fig. 10.

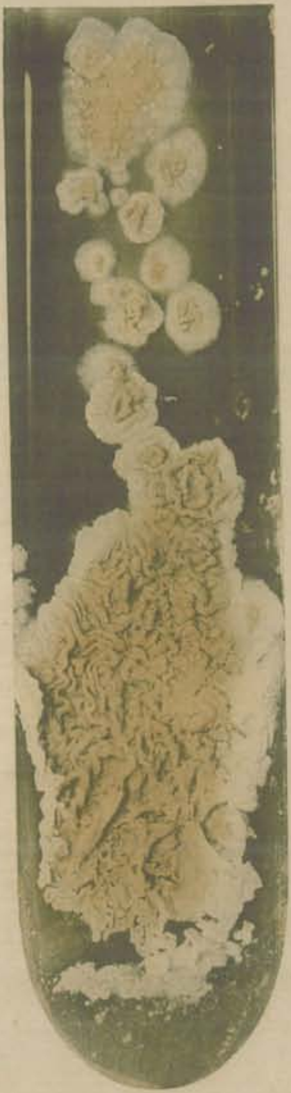

Fig. 9.

PLATE V.

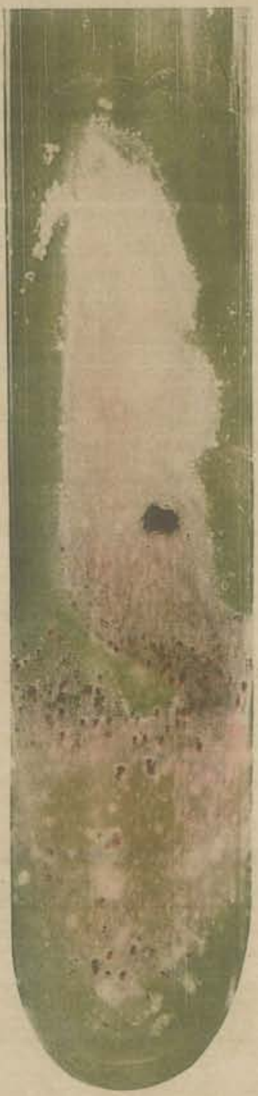

Fig. 12.

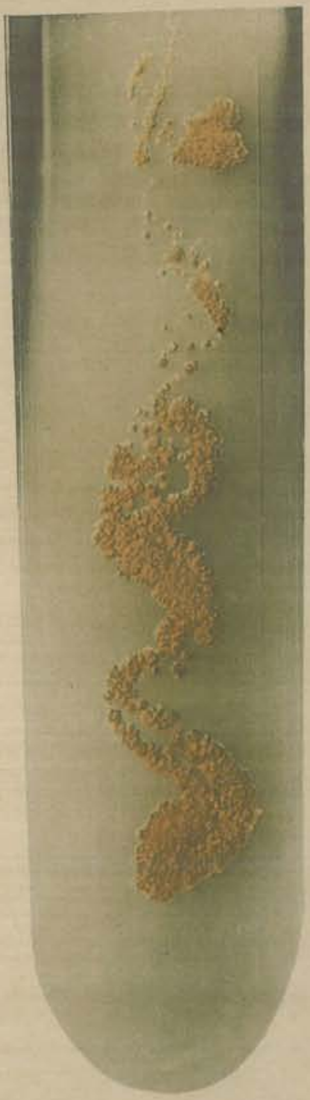

Fig. 11.

PLATE VI.

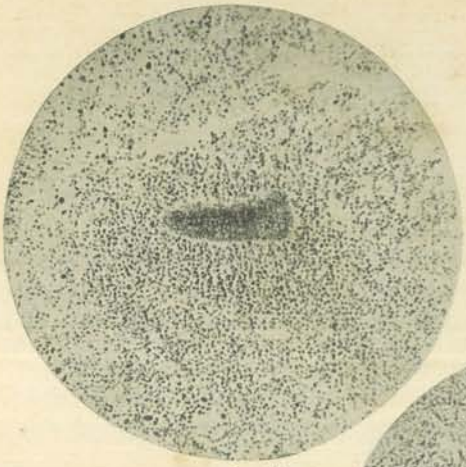

FIG. 13.

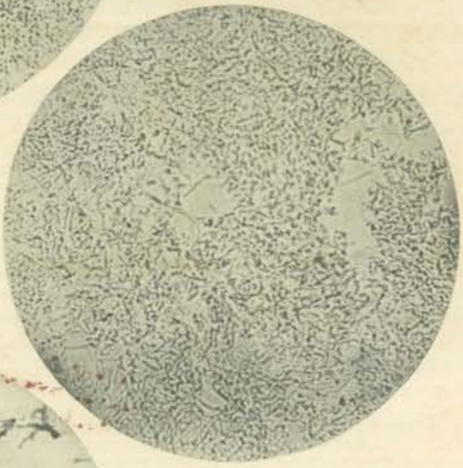

FIG. 14.

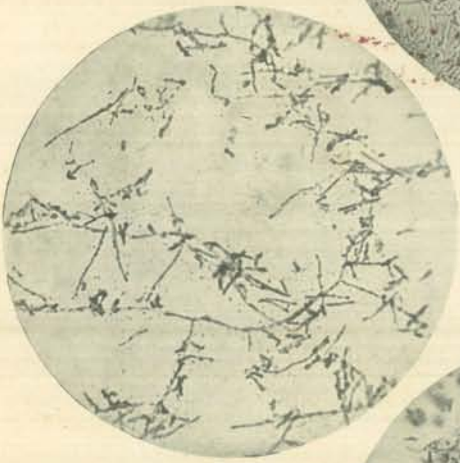

FIG. 15.

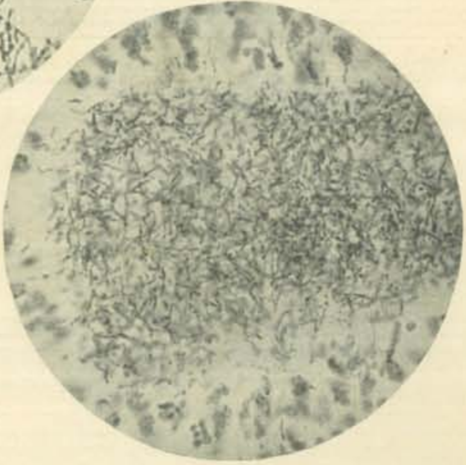

FIG. 16.

PLATE VII.

TRICHOCEPHALIASIS.

(WITH A REPORT OF FOUR CASES, INCLUDING ONE FATAL CASE.)

By W. E. MUSGRAVE and M. T. CLEGG, with a
bibliography by MARY POLK.

(From the Biological Laboratory and the Library, Bureau of Science.)

OUTLINE.

- INTRODUCTION.
- CASE REPORTS.
- LITERATURE OF THE DISEASE.
- TRICHOCEPHALIASIS.
  - Synonyms.
  - Definition.
  - Etiology.
    - Contributing causes.
    - Trichocephalidæ (by F. H. Garrison).
      - General discussion of the genus.
      - Trichuris trichiura.
      - Modes of transmission.
        - Direct.
        - Indirect.
          - Water.
          - Food.
          - Insects (flies, etc.).
          - Soil.
          - Dust, clothing.
          - Air.
          - Animals.

TRICHOCEPHALIASIS—Continued.
  - Etiology—Continued.
    - Trichocephalidæ—Continued.
      - Pathogenesis (parasitism).
        - General.
        - Manner of infection.
  - Pathology of the disease.
  - Symptoms.
    - Incidence.
    - Clinical varieties.
      - Intestinal.
      - Appendicial.
      - Mild.
      - Severe.
  - Trichocephaliasis of animals.
    - Diagnosis.
    - Prognosis.
    - Prophylaxis.
    - Treatment.
    - Bibliography.

INTRODUCTION.

Our own experiences and a careful review of the literature of whipworm infections, convinced us that the subject has much more importance in human pathology than is generally assigned to it.

For this reason we have decided to publish four of our cases in detail, review the most important articles in the literature and then discuss the question of trichocephaliasis in monographic form with special reference to the disease-producing powers and clinical manifestations of infection with these parasites.

While it is true that the majority of investigators who have published the results of original work have attributed pathogenic properties to these parasites, and although these observations are supported by such authorities as Seifert, Stiles, Metchnikoff and others, to-day the majority of text books on medicine barely mention these infections and in general state that they are of little or no importance from a medical standpoint.

CASE REPORTS.

CASE I.—*Trichocephaliasis with severe progressive secondary anaemia followed by death; autopsy.*

L. G. N., male Filipino, 24 years of age, was admitted to St. Paul's Hospital August 9, 1908, died September 16. *Family history:* Father and mother are both living and in good health; two brothers died of smallpox. *Previous illness:* As a child the patient had chickenpox, a few mild attacks of "malaria," and five years ago suffered from an abscess of the parotid gland. *Present illness:* Three weeks before admission the patient began to feel dizziness, weakness, slight fever in the afternoons and ringing in the ears. This condition gradually grew worse and about ten days before admission he noticed beginning œdema of the ankles, hands, and face.

On admission the patient complained of shortness of breath, great weakness, ringing in the ears, palpitation of the heart, nausea, lack of appetite, dyspeptic symptoms and slight diarrhœa.

Examination.—The patient is a rather large, well-developed Filipino with marked œdema of the extremeties and face, marked pallor of the mucous membrane and rapid, shallow respiration. The circulatory system appears normal, except for a slight hæmic murmur heard at the apex of the heart and an increased pulse rate to 110, when the patient is in an upright position.

Blood examination as follows: Red blood cells, 1,800,000; leucocytes, 10,000; hæmoglobin, 20 per cent. Differential count: Mononuclear cells, 65 per cent; polynuclear cells, 30 per cent; transitional, 5 per cent. There are no nucleated red blood cells and but a moderate poikilocytosis. No eosinophile cells are present in a count of 500.

Respiratory system, negative. *Alimentary system* shows the following changes: Lips and other mucous membranes extremely pale, tongue large and flabby with a dark, almost black, streak down the center. Nothing abnormal is found in the abdomen, excepting a slight accumulation of fluid; the liver is slightly enlarged; the spleen is not palpable. The examination of the stomach contents shows no abnormality; examination of the stool after a saline cathartic shows enormous numbers of the ova of *Trichuris trichiura.* The urine is normal by chemical and microscopic examination. *Nervous system:* There is no pain, and the reflexes are normal. *Locomotor system:* Œdema and considerable flabbiness of the muscles are the only abnormalities noted. *Cutaneous system:* The skin appears normal and there is no enlargement of the superficial lymphatics. The patient's condition grew gradually worse from the time of admission with accentuation of the following symptoms: Œdema became general and progressed until death; the anæmia was also progressive, and the same general character of blood picture was maintained until the end. A count made a few days before death showed the following: Red cells, 844,000; hæmoglobin, 18 per cent. At this time there were still no nucleated red cells and no eosinophile cells to be found. Nausea, from which the patient suffered upon his admission, became more constant and toward the end vomiting was a very distressing and unmanageable symptom. The nervous and mental symptoms became more marked and during the last week of illness there was active delirium. The patient finally died of asthænia.

There were no hæmorrhages at any time and no severe diarrhœa. Repeated examinations of the stool always demonstrated very large numbers of *Trichuris* eggs. The temperature was practically normal throughout the course of the disease. Three separate attempts were made to dislodge the parasites, which were the only discoverable cause of the anæmia, the following substances being used for this purpose: Thymol in doses of 8 grams on two occasions and the well-known eucalyptus-castor oil and chloroform mixture on one occasion. A few *Trichuris* were obtained with two of these treatments, about 15 or 20 in all being secured. The stool from the third treatment was unfortunately destroyed without examination. Other treatment administered consisted in stimulation and in attempts to build up the nutrition.

Autopsy was performed one hour after death by Dr. Gilman and his report of the findings is as follows:

Body of a sparely nourished Filipino 157 centimeters long; rigor mortis absent; body still warm; pupils moderately dilated; equal; distinct yellowish tinge of sclerae; the entire body has a yellowish tinge. There is no general glandular enlargement; abdomen flat; no scar on penis. Shins clear.

Subcutaneous fat is present in good amount, is of a lemon-yellow color, more brilliant than normal. Muscles are practically of normal color.

Peritoneum is everywhere smooth and glistening. The mesenteric and omental fat is present in good amount, similar in shade to the subcutaneous fat. The general visceral arrangement is normal. Coils of small bowel are in general contracted, small, appendix region is free from adhesions. Bladder is distended with urine extending 11.5 centimeters above the symphysis. Diaphragm at the upper border of the 5th rib on the left, lower border of the 4th rib on the right.

Pericardium is smooth and glistening, contains 1 or 2 cubic centimeters of clear fluid. Heart is firmly contracted, measures 10.5 centimeters from the auriculoventricular ring to apex, surface smooth, sub-epicardial fat well-developed. The right side of the heart is practically empty, but for a small amount of fluid blood. Valves are normal and competent. The left side of the heart contains a small, dark, post-mortem clot. The mitral valves are normal as are the aortic. Base of the aorta is smooth and elastic. The wall of the left ventricle measures 2 centimeters at its thickest portion and the right measures 0.6 centimeter. The heart muscle is of a firm, reddish-brown color. Heart weight 300 grams.

Lungs: The left pleural cavity is obliterated, the lung being adherent to the chest wall and diaphragm by firm, old, fibrous adhesions. The lung is apparently crepitant everywhere, is pale and on section is air-containing throughout, of a pasty yellowish-gray color. The right lung lies free in its pleural cavity except at the base, where it is adherent to the diaphragm; it presents a similar appearance to the left. Apparently air-containing throughout. On section similar to opposite lung.

Spleen is small, measuring 7.3 by 4.5 by about 2.5 centimeters, surface smooth, color dark grayish-purple. On section there is a decided increase in the connective tissue. The pulp is moist, of a brownish color. Spleen weighs 35 grams.

Kidneys: The left kidney measures 10 by 6 by 4 centimeters, its capsule strips readily, leaving a smooth, pale yellowish surface somewhat mottled with areas of red. On section the cortex measures, 0.6 centimeter, entire organ is of a pale yellowish color, contains a very small amount of blood. The right kidney measures 9.8, by 5.5 by 3.5 centimeters, is similar throughout to opposite organ. Combined weight of the two organs is 270 grams. Suprarenals are normal.

Pancreas is firm, of a yellowish color. On section it is somewhat pale, although apparently normal.

Liver measures 24 by 14 by 8 centimeters, surface is smooth, edge sharp, organ is somewhat soft and putty-like. On section the parenchyma is of a brownish color, homogeneous. Gall-bladder contains several cubic centimeters of dark, slightly inspissated bile. Duct patent. Weight of liver is 1,020 grams.

Bladder measures 15 by 12 centimeters, walls are stretched and thinned. It contains a large amount of clear, amber-colored urine. Mucosa is very pale, otherwise normal. Prostate apparently normal.

Stomach: Mucous membrane extremely pale with small, hæmorrhagic areas near the pyloric end; otherwise the organ appears normal.

Small intestine: Contents, greenish mucus. The mucosa shows the same pale condition. Peyer's patches and solitary follicles prominent, but not congested. Numerous *Trichuris trichiura* are present, the greater number being found in the lower part of the ileum.

Large intestine: On opening the ileocæcal valve two hundred trichiuris are counted. These parasites extend the entire length of the gut. The mucosa of the descending colon shows a few healed amœbic ulcers. With the exception of the extremely pale condition of the mucosa, the organ appears normal.

Anatomic diagnosis.—Severe grade of secondary anæmia.

Specimens of the worms were submitted to Mr. G. F. Richmond, chief of the chemical laboratory, for determination as to the presence of pigments of blood origin and he reports that no such pigments are found.

Dr. Philip E. Garrison, medical zoölogist, Biological Laboratory, Bureau of Science, reports as follows:

"The whip-worms received on September 16 have been carefully examined and compared with specimens identified in Dr. Stiles' laboratory in Washington. They appear to agree in every material character with *Trichuris trichiura* (Linnaeus 1761)=*Trichocephalus dispar* Rudolphi, 1801. The specimens are No. 258 in the Bureau of Science Helminthological Collection."

CASE II.—*Severe infection with whip-worms, with diarrhœa, muscular cramps, dizziness, œdema and indigestion; patient left hospital after ten days observation.*

F. E., male Filipino, age 22, was admitted to St. Paul's Hospital March 10, 1906, and left March 21. His *family history* and the *history of previous diseases* give no data of importance. *Present illness:* For about six months previous to admission the patient has suffered from diarrhœa of a somewhat intermittent character. The stools were only one or two on some days, but generally they were from five to ten or more in twenty-four hours, being soft and pasty. Other symptoms during this time were dizziness, weakness, palpition of the heart, tinnitus aurium, cramps in muscles of the legs and chest, anorexia and indigestion.

On admission the patient complained of weakness, shortness of breath, palpitation of the heart, nausea, diarrhœa, ringing in the ears, partial loss of voice and melancholic tendencies.

Examination shows a pale, somewhat emaciated Filipino with moderate œdema of the feet and legs. Examination of the circulatory system demonstrates a weak pulse of 110 in the upright position: the arteries are soft and there is a soft murmur at the apex of the heart. The spleen not palpable, and blood examination is as follows: Erythrocytes, 2,400,000; leucocytes, 9,000; hæmoglobin 23 per cent.

There are no nucleated red cells and the differential leucocyte count shows a slight relative increase in large mononuclears. There is no eosinophilia. The respiratory system appears normal. Examination of the alimentary system gives the following details: Tongue, large and flabby with teeth marks on the edges, but no dark streak in the center. The abdominal examination is negative and the stool contains very many ova of *Trichuris trichiura.* The urinary system (including urine examination), the reproductive, cutaneous, and locomotor systems appear normal, except for moderate œdema of the lower extremeties. The reflexes are present and nothing abnormal is found upon examination of the nervous system.

During the patient's ten days' stay in the hospital, two unsuccessful attempts were made to remove the *Trichuris*. Both thymol in 6 gram and santonin and calomel in 0.250 gram doses were used. The patient left the hospital in a worse condition than when he entered.

In this case repeated and careful examinations were made and the data obtained could only be explained by assuming the cause of disease to be *Trichuris trichiura*.

CASE III.—*Trichocephaliasis with severe secondary anæmia; under observation and treatment for one month without improvement.*

D. V., a male Eurasian from Singapore came under our observation in September, 1904, and left the Philippine Islands in October of the same year. The family history and history of previous illnesses of this patient are unimportant.

Present illness.—About one year after arrival in the Philippine Islands the patient began to notice that he was becoming "anæmic," with shortness of breath and palpitation of the heart. About one month before he consulted us, diarrhœa developed and there was some œdema of the legs. At the time he came under our observation the principal subjective symptoms were dizziness, with shortness of breath and palpitation of the heart upon exertion, indifferent appetite, with nausea more marked in the morning, occasional vomiting, and moderate diarrhœa. There was a general feeling of "nervousness" and tendency toward melancholia.

Examination.—A rather severe secondary anæmia was present which could not be explained, except by the presence of a rather severe *Trichuris* infection. The stools after a saline cathartic often contained as many as 20 eggs in one field of the microscope, an AA objective and No. 4 ocular being used.

The blood examination was as follows: Erythrocytes, 2,800,000; leucocytes, 6,400; hæmoglobin, 36 per cent.

There were no nucleated red cells and the differential leucocyte count was approximately normal.

One unsuccessful attempt was made to dislodge the parasites by thymol. Good food, tonics, and general hygiene were prescribed, but the patient did not improve and he left the Philippine Islands about one month after we first saw him.

CASE IV.—*Embolism of the left coronary artery caused by an adult Trichuris trichiura.*[1]

It has not been possible to obtain a clinical history of very much importance in this case. The patient was a Filipino boy, 17 years old, and had been ill for about a week. For approximately the first five days he complained of pain in the chest, cough, shortness of breath, and he vomited once or twice. Slight diarrhœa developed and continued throughout the trouble. Pulse 130, temperature at first from 38° to 39°. Two days before death the symptoms became very much aggravated; vomiting more frequent, temperature 40°.5. Death occurred suddenly.

Autopsy (twenty-three hours after death).—Petechial hæmorrhages in skin of shoulders and occasional ones over the rest of the body. No glandular enlargements.

Lungs: Lower lobes much congested, dark, grayish-red in color. Center of outer surface of left lobe shows a hæmorrhagic infarct about 4 centimeters in diameter, penetrating about 3 centimeters into the lung substance. Lower edge of right lower lobe has a large infarct about 11 centimeters in length and about 6 centimeters broad. On section no embolism could be found in the arteries.

---

[1] This case is not reported as one of importance in elucidating the question of the pathogenicity of whip-worms, but it is mentioned as being a very curious finding for which we have no explanation to offer.

Heart: Very slight atheromatous patches in arch of aorta. The left coronary artery contains an adult *Trichuris trichiura*, with about one-third of the posterior portion remaining free in the aorta.

Liver: The liver is friable, dark red in color (slight post-mortem change). The *spleen* is dark red, slightly mottled, and of firm consistency. *Kidneys* congested.

Moderate injection of the mucous membrane of the large intestine, which contains a small amount of mucus; a number of *Trichuris* were found in the cæcum.

Anatomic diagnosis: Embolism of the left coronary artery due to adult *Trichuris;* hæmorrhagic infarcts of the lower lobe of either lung.

Numerous other cases of *Trichuris* infection much less severe, but with suggestive symptoms, could be mentioned, but in them the diagnosis is not so clear and they will only be considered in the general discussion in the second part of this paper.

GENERAL REVIEW OF THE LITERATURE.

The first description of the parasite which we now recognize as *Trichuris trichiura* (Linnaeus 1761) was that of Morgagni(61) who found the worms in the cæcum of a man at autopsy. Röderer(73), in collaboration with his students, made additional contributions to the description of the parasite, and Büttner (1761) examining their specimens and mistaking the posterior for the anterior end of the parasite named it *Trichuris*. Linnæus (1771) introduced the name *Ascaris trichiura*. Goeze(34) recognized Büttner's error in thinking the smaller end to be the head of the parasite and changed the name from *Trichuris* to *Trichocephalos*. According to Blanchard(8) Morgagni, Röderer, Wagler, Happ, and Wristberg thought there were two species of these worms, but Müller (1778) showed the two kinds to be male and female; Schrank (1788) recognized the parasite under the name of *Trichocephalus hominis*, and the same name was used by Gmelin (1789); Rudolphi (1801) described the parasite under the name of *Trichocephalus dispar* and this name has been the one in most common use until within the last few years.

Owing to the adoption of different rules of nomenclature there is at present considerable difference of opinion among zoölogists as to the correct name of the parasite. Stiles maintains *Trichuris trichiura*, while most of the European authors adopt *Trichocephalus trichuris*.

Without entering into the discussion, we have decided in this report to use the name recommended by Stiles.

Barth(4) reports a case of severe infection with *Trichuris* as the only explanation of severe meningitis-like symptoms in a patient. This is perhaps the first report in which a pathogenic rôle in human beings has been attributed to this parasite.

Davaine(19) examined a large series of stools in Paris and concluded that probably one-half the people of that city harbor this parasite.

Gibson(32) reports an interesting case of severe nervous symptoms with paralysis in a girl who had a very severe *Trichuris* infection. Calomel 0.065 gram and rhubarb powder 0.65 gram were given night and morning for some days. "On two occasions the child passed a small chamber vesselful of worms; species, *Trichocephalus dispar.*" More worms were passed on another date and following this, the child rapidly recovered.

Pascal (67) reports the case of a girl, 4 years old, who died of brain symptoms simulating meningitis. Many *Trichuris* were found in the intestine at autopsy and no pathologic changes were discovered. The author believed the parasites to have been the cause of death.

Burchardt (14) reports two cases in which he regarded *Trichocephalus* as the causative agent. Vomiting, diarrhœa, headache, dizziness, and marked anæmia were present in his first case. There was slight improvement upon treatment, followed by relapse with icterus, bloody vomit, aphonia, and marked anæmia. Complete recovery followed the expulsion of a large number of the worms. Burchardt's second case was similar to the first, excepting that the symptoms including the nervous ones were much less marked.

Mégnin (56) pointed out the fact that dogs which harbor large numbers of a *Trichuris* suffer from a pernicious anæmia.

Lutz (53) working in Brazil, found eggs in the stools of man, pigs, and cats. In man, about one-third of the specimens examined contained the ova.

Erni (24) believed the Trichuris to be one of the causes of beri-beri.

Grassi (35) describes the swallowing of *Trichuris* eggs by a student who 28 days later found the first eggs in his stools.

R. Blanchard (9) in a review of the subject of *Trichuris* infections states that Vix, Leukart, and Brumpt all give observation of the transfixation of the mucosa of the caecum by *Trichuris* and believes that this definite fastening of the worms explains their constant absence from the fæces in infected cases. However, Klebs (50), Heller (45) and Wichmann (89) do not believe that the worms attach themselves to the mucosa, but state that they are maintained in place by a mucus capsule resting upon the mucous membrane.

Moosbrugger (59) reports three cases. The first was in a boy a year and a half old who had a severe diarrhœa and with the usual symptoms accompanying the latter. During an attack of bronchitis with fever the eggs of *Trichuris*, which had been very numerous in the stools, disappeared. The author's second case was in a three year old boy with symptoms similar to those in the first. The patient died of croup and at the autopsy 442 male and 445 female worms were removed from the bowel. The mucous membrane was pale in some places and in others there were zones of congestion, with red spots and some erosions and ulcerations in others. The third case was that of a girl three and half years old, who had suffered for six months with severe diarrhœa of twenty or more stools daily. The stools were tough in consistency and usually contained some blood. There were 1,650 *Trichuris* eggs in one cubic centimeter of fluid stool. The child was very anæmic, but recovered under treatment. Moosbrugger considers the parasites to be the cause of the symptoms in his cases.

Boas (11) considered the *Trichuris* to be the cause of severe chronic diarrhœa, emaciation and anæmia in his patient, who was a man 71 years old.

Huber (47) considers the clinical significance of this parasite to be generally underestimated. He notes the presence of the worms in the cæcum, appendix, and occasionally in the ileum. The symptoms depend upon the severity of the infection and are local (diarrhœa) and reflex (aphasia, etc.).

Askanazy (3) demonstrated an iron-containing pigment in the intestinal epithelial cells of *Trichuris* and concluded it to be a blood-sucking parasite. He also showed that the parasite attached itself to the intestinal wall by piercing a loop of mucosa or by inserting the head into the glandular tubules of the mucosa. He believed that during certain diseases, or after death of the host, the parasites disengage themselved from the mucous membrane and that this fact explains why at autopsy they are usually found free in the intestine. Becker (5) in accepting the hypothesis of Askanazy, explains his failure to secure the worms when his patient was treated with benzine, by stating that the worms were killed in place and so remained attached to the mucosa.

Morsasca (62) reports one case of severe progressive anæmia accompanied by abdominal pains, nervous symptoms, and diarrhœa and considers that *Trichuris*, which were present, to be the cause of the condition.

Federolf (27), a Russian military surgeon, notes that Russian authors have repeatedly called attention to the serious symptoms which may be produced by *Trichuris* infections. He reports one case in which the prominent symptoms were psychic depression, slight diarrhœa, retention of urine, fever of intermittent character, nausea, and palpitation of the heart. Treatment by santonin was followed by the disappearance of the eggs from the stools and the complete recovery of the patient.

Heine (43) encountered *Trichuris* in many sick deer and in two of the animals which he found dead the presence of these parasites was the only condition which could explain the result. Hausmann (42) believes that certain of the symptoms of infection with this parasite point to the production of some form of toxin. Guinard (41) reports finding nematode worms in the cæcum at operations for appendicitis.

Metchnikoff (57) considers both the clinical and pathologic facts to be convincing of the important rôle of eelworms and whip-worms in appendicitis. Guiart (39, 40) insists upon the important pathogenic rôle of *Trichuris* in human pathology. The parasite fixes itself on the mucous membrane of the cæcum or appendix and becomes an inoculating agent of bacteria. In one case of appendectomy an adult *Trichuris* was found attached to the mucosa of the appendix and the author believes it to have been the cause of the disease.

Girard (33) reports a case of appendicitis with general peritonitis due to infection with *Trichuris* (*Trichocephalus hominis*). The patient was a girl, 8 years old, who was recently convalescent from typhoid fever. She was re-admitted to the hospital suffering from diphtheria and a vaginal discharge. Under antitoxin treatment there was recovery from the diphtheria. Symptoms of acute, severe appendicitis developed and the appendix was resected on the fourth day. At operation a general peritonitis was encountered and after resection of the appendix and drainage, complete recovery resulted. The appendix was fixed *en masse* and sectioned. In general the organ showed but slight pathologic change except in the distal third where there was rather severe inflammation. Section in this area showed partial occlusion of the lumen caused by two of the adult *Trichuris* which were firmly attached to the mucosa. The author describes and illustrates the inflammatory zone around the attachment of the worms to the mucosa and, although no perforation is mentioned, he considers the peritonitis to be due to the condition of the appendix. Finally, Girard believes he has demonstrated the penetrating powers of the whip-worm; he states that the parasites play a septic rôle at least by transmission of pathogenic bacteria and he believes with Metchnikoff, that these parasites may cause inflammatory lesions which may lead to grave consequences.

Schiller (75) reports a case of heavy infection with *Trichuris* in which high fever was a symptom. Hemmeter (46) considers that single specimens of the parasite do not cause symptoms, but if larger numbers occur in the colon, diarrhœa and nervous symptoms may appear.

Becker (5) reports two cases of *Trichuris* infection. In the first the patient was a woman suffering from chronic progressive anæmia with dizziness, cramps in the muscles, abdominal pain, and palpitation of the heart and the stools contained many *Trichuris* eggs. Physical examination was negative. At the time she came under the author's observation the blood examination showed as follows: Marked poikilocytosis and macrocytes were numerous; erythrocytes 3,456,000; leucocytes 6,250; hæmoglobin 35 per cent. After three week's observation it was: Erythrocytes 3,200,000, leucocytes 6,000, hæmoglobin 25 per cent. The differential count of the leucocytes showed: Polymorphonuclears 69, lymphocytes 26, mononuclears 3, eosinophiles 2. There were no nucleated red cells. Numerous *Trichuris* eggs were present in the stools. The patient was treated with eight enemas of solutions of benzin. No parasites were found during or after these treatments, but the eggs disappeared from the stools and were not again seen. The patient rapidly recovered after the disappearance of the eggs from the stools. The author's second case was that of a woman 26 years old suffering from chronic progressive anæmia, palpitation of the heart, dizziness, nausea, and diarrhœa. The stool contained numerous *Trichuris* eggs. The physical examination was negative. The blood examination showed: Erythrocytes, 2,852,000; leucocytes, 8,700; hæmoglobin, 25 per cent. Normoblasts were numerous but megoloblasts were not present. There was some improvement in this case under treatment by arsenic and iron. The patient left the hospital before further observation could be made. Becker believes the *Trichuris* to be responsible for the condition in both these cases and furthermore compares its action with that of *Agchylostoma* and the *Dibothriocephalus latus.*

Ward (88) states that since Askanazy has shown the occurrence of hæmoglobin in the alimentary canal of these worms, the fact that they nourish themselves on the blood of the host can not be doubted.

Sandler (74) reports a fatal case in a boy twelve years old. The patient when admitted to the service complained of fainting spells, anæmia, weakness, palpitation of the heart, fever of an irregular, intermittent type, yellow and brownish spots on the legs, headache, nausea, vomiting, diarrhœa with blood at times, abdominal pains and tinnitus aurium. On examination there was marked anæmia, hæmic murmur of the heart, and weak, rapid pulse. The spleen and lymphatics were not enlarged. Blood examination showed: Erythrocytes, 1,200,000; leucocytes, 30,600; hæmoglobin, 28 per cent. There was poikilocytosis, but no nucleated red cells. The stools contained eggs of *Trichuris.* After about two weeks of treatment and observation the blood examination was as follows: Erythrocytes, 690,000; leucocytes, 14,000; hæmoglobin, 20 per cent. The patient's condition grew progressively worse with accentuation of the principal symptoms mentioned, and others also developed. There was bleeding of the nose, the sense of fear became marked, fever became more severe, reaching 39° in the afternoons, and for some time before death which occurred in coma, there was delirium and very frequent vomiting. The diarrhœa improved so that the bowels were practically normal for some time before death. Autopsy could not be obtained, but the author is convinced that *Trichuris* was the etiologic factor in the condition.

French and Boycott (28) in reporting upon the prevalence of *Trichuris* infections in the patients in Guy's Hospital, London, makes the following observations. Stools of 500 patients were examined and *Trichuris* eggs were found 39 times or 7.8 per cent. The infection was rare in children under 5 years of age and was about equal in the sexes. The authors also compile the statistics as to prevalence from the following sources: Leuckart (52) in Erlangen 11.1 per cent, Erlangen insane 100 per cent, Dresden, 2.5 per cent, Kiel 32.2 per cent; Cobbold (17) in Dublin 90 per cent, Greenwich 69 per cent; Davaine (20) in Paris 50 per cent, Naples 100 per cent; Blanchard (9) in Bâle 23.6 per cent; Garrison, Ransom, and Stevenson (31) in 10.8 per cent of insane; Ashford, King, and Igaravidez (2) 6 per cent; Boycott (12) in Cornish Miners 79 per cent. Garrison (30) working in the Philippine Islands found the infection in 59 per cent of adult prisoners.

Osler(65) states that "The *Trichocephalus* rarely causes symptoms." He notes without comment the recent observations in which severe anæmia has occurred in connection with infections with this parasite. Allen J. Smith(80) considers the parasite to be of little pathologic importance, stating that apparently it does but little damage and practically never gives rise to appreciable symptoms of its presence. Emerson(23) states that "This parasite is harmless as a rule, but may cause enteritis and the severest and even fatal anæmia."

Poledne(68, 69) reports one case. The patient was a sailor who was admitted to the hospital suffering from fever and severe diarrhœa. The fever was typhoid in character, but careful examination by modern laboratory methods gave negative results for typhoid, paratyphoid, Malta fever, and tuberculosis. Anæmia, emaciation, and nervous symptoms were present. The blood showed a slight leucocytosis and a relative eosinophilia. There were numerous ova of *Trichuris trichiura* in the stools. The fever and diarrhœa subsided after treatment by thymol and by benzine enemas, the eggs disappeared from the stools and a rapid and permanent cure followed.

Vix(86) considers the parasite to be pathogenic and states that it may produce ulceration of the intestinal mucosa. Rippe(72) reviews the literature of *Trichuris* infections and reports two cases occurring in Russia. His first patient was a woman who had been ill for three years. The important symptoms were nausea and vomiting, anorexia, weakness, dizziness, muscular pains particularly in the legs, slight diarrhœa, and melancholia. On examination there was emaciation, marked pallor of the mucous membrane and some abdominal distension with tenderness over the cæcum. The stools contained mucus and numerous eggs of *Trichuris*. After treatment by thymol the eggs disappeared from the stools and the patient made a rapid and permanent recovery. The second case was in a man who was suffering from a purulent pleuritis, with frequent epileptoid seizures, diarrhœa, muscular cramps, nausea, and restlessness. There were numerous eggs of *Trichuris* in the stools. The patient died and at autopsy the brain was normal, except for slight œdema of the meninges; the mucous membrane of the cæcum and lower portion of the small intestine was hyperaemic and contained *Trichuris trichiura*. Rippe considers *Trichuris* to be a pathogenic parasite and that infection with it must be considered in making diagnoses in conditions showing intestinal and nervous symptoms. The author found the eggs in 42.93 per cent of 184 cases of parasitic infection of the intestine in Russia.

Stiles(82) treats the pathogenicity of this parasite in a conservative manner. He recognizes a lack of symptoms in the majority of light infections, but on the other hand this author makes the statement "that severe infections do not produce injury is not in accordance either with probability or with recorded observations." Again he states that "several cases of severe anæmia have been recorded within recent years which were, apparently justly, attributed to heavy infections with whip-worms." Kahane(48) considers the parasite to be pathogenic. He states that it can cause ulceration of the intestinal mucosa and that the head may penetrate the walls of the bowel to the muscular coat.

Sir Patrick Manson(54) considers *Trichuris* infestation of no practical moment and that, so far as known, the parasites give rise to no serious pathologic lesions. Manson and Shipley(55) state that so far as is known *Trichuris* has very little pathologic significance, except when it perforates the intestine. These authors call attention to reports in which nervous symptoms have been associated with a high degree of infection. According to the same authors "several cases of anæmia (some fatal) are reported as caused by the presence of this parasite, the blood showing a fall in the number of red cells, marked poikilocytosis, and the appearance of nucleated red cells principally of the normoblastic type." Eosinophilia has been noted, but is not the rule.

Braun (13) considers *Trichuris* to be pathogenic. Seifert (78) states that from the evidence of recent years it is necessary to remove *Trichuris* from the list of commensal parasites and place it among those pathogenic for man, and that the prognosis is grave in some severe infections.

TRICHOCEPHALIASIS.

SYNONYMS.—Whip-worm infection, Trichuriasis.

DEFINITION.—An infection with whip-worms, usually confined to the large intestine, less frequently to the appendix and ileum and occasionally by perforation invading other parts of the body. In light infections there are no pathologic changes or symptoms of importance, but the heavier infections are characterized by anæmia, which may be very severe and even fatal and by nervous and gastrointestinal symptoms.

ETIOLOGY.—Contributing causes: The ordinary causes which usually are considered as influencing infections probably play a less important rôle here than with many other diseases.

The geographic distribution of the infection is cosmopolitan. It is particularly prevalent in the Philippine Islands.

Sex.—Practically all authors recognize the much more frequent infection in females. Stiles and Garrison (83) in 3,457 cases found 12.13 per cent of infections in females and 10.08 in males.

Age.—It is generally recognized that infections are most prevalent during childhood and gradually grow less with advancing age.

Garrison, Ransom, and Stevenson (31) in 500 examinations noted this gradual decrease of infection with age, and Stiles and Garrison (83) found the following percentages of infection according to age: Under 15 years 13.01; from 15 to 30 years 10.09; from 31 to 50 years 8.65 and over 50 years 4.65. Garrison's (30) statistics in the Philippines were based entirely upon examination of specimens from adults and in our service the number of recorded examinations for children is too small to make statistics of value. However, we have seen several instances of infections in breast-fed infants, in one case the child being less than 3 months old.

Race and nationality.—In general it may be stated that the infection is more frequent among the colored races than it is in the Caucasian. Stiles and Garrison noted particularly the preponderance of infections in the American negro over that of the white races of the same country. Our records show a much higher percentage of infection in native Filipinos than is found in the foreign residents of the Caucasian race resident in Manila. In Stiles and Garrison's statistics, Irish born patients showed a higher percentage of infection than did any other nationality resident in the United States.

Residence.—The infection is more common in rural districts than it is in cities, no doubt largely because of the better methods of disposal of fæces in cities.

Occupation.—The infection is more frequent among soldiers, laborers and others whose manner of life and occupation brings them into contact with faecal infected substances.

Overcrowding with its usual insanitary surroundings may readily be inferred to be a facter in incidence.

Climate.—It is generally stated that the infection is more frequent in warm climates.

Gastrointestinal condition.—There are no statistics available, but it is probable that it is not a factor in the incidence of this infection.

Environment and mode of life.—After all is said regarding the influence of race, sex, etc., upon the prevalence of this infection, it is probable that the question of infection or noninfection is almost entirely due to the mode of life of any given individual or community. In other words, it is a question of exposure, which in the vast majority of instances occurs only in those who are ignorant, or whose personal hygiene is otherwise very faulty. *In a sense, it seems to us, that the prevalence of whip-worm infections in a community is, to a certain extent at least, an index of the intelligence and cleanliness of its citizens.* This statement makes the assumption of what is probably a fact, that physiologic predisposition to infection with this parasite (except perhaps in children), if it exists at all, surely does so to a very minor degree.

Stiles and Garrison in discussing the question of physiologic predisposition in females state that "the relative frequency of a given parasite, or of helminthiasis in general, among males and females is apparently not so much a question of physiologic predisposition of the sex toward the parasite, as it is a question of the relative intimacy existing between the average daily life of the sex and the more concentrated infectious material."

In the case of whip-worm infections it seems to us that this statement applies not only to a question of sex, but that it explains many of the differences noticed under predisposing causes. Carrying this statement to its logical conclusion, we may say that race, sex, occupation, etc., as such, probably are not factors in the incidence of the infection, except to the extent in which they harmonize with the person's exposure to sources of infection under a given mode of life.

TRICHURIS.[2]

This *genus* is easily recognized by its peculiar whip-worm shape; the thick posterior portion and the long, slender anterior portion representing the stock and the lash respectively. The anterior extremity bears a small, round, mouth opening, behind which lies a small, funnel-shaped oral cavity. The long, thread-like œsophagus extends throughout the greater portion of the anterior, slender part of the body and enters the intestine which, in a folded course, reaches the posterior extremity of the body to find exit at a terminal anus in the female, and at the common genito-anal orifice in the male. The cuticle is striated transversely, except on the ventral surface where a longitudinal band, set with minute papillæ, extends from the anterior to the posterior extremities. The thick posterior portion of the body contains the intestine and the genital organs. In the female it is straight or slightly bow-shaped; in the male it is more or less closely coiled.

Male organs.—The testicle is single and consists of a long, coiled and folded tube which fills the greater part of the caudal portion of the body. A short, broad *vas deferens* turning abruptly caudad from the anterior end of the testicle enters a dilated portion of the genital tube (*vesicula seminalis*) which, in turn extends posteriorly to the cirrus or spicule. The spicule is single, highly developed and lies in a sheath or cirrus pouch, both sheath and spicule being protrusible for a considerable distance through the cloacal orifice.

Female organs.—The ovary is simple, tubular, with its extremity attenuated into a slender oviduct which enters the posterior end of the more expanded uterus. From the anterior extremity of the uterus, the slender, more or less coiled vagina leads to the genital pore which is situated on the ventral surface at about the junction of the slender, anterior and the thick, posterior portions of the body.

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[2] These diagnoses of this genus and species, furnished by Dr. Philip E. Garrison of this laboratory, are taken from various authors, chiefly Leuckart, with the purpose of furnishing for medical men a description of the parasite, not too technical, but rather more detailed than that usually given in medical publications.

The ova are barrel-shaped and are characterized, as are those of *Trichosoma*, by the little colorless plug which closes each end of the brownish shell.

Habitat.—The cæcum and, less frequently, the colon and ileum of certain mammals.

Several species of *Trichuris* are recognized for different hosts, namely, *Trichuris trichiura* of man and apes; *T. affinis* of sheep, goats, and cattle; *T. depressinsculus* of the dog and fox; *T. unginculatus* of the rabbit; *T. crenatus* of the pig. These species are distinguished morphologically chiefly by the size and structure of the spicule and its sheath.

Trichuris trichiura (Linnæus, 1761).

Male, 40 to 45 millimeters long; spicule, 2.5 millimeters long; sheath covered with small, evenly distributed papillæ. Female 40 to 50 millimeters long, length of slender anterior portion to length of thick posterior portion as 3 to 2. Mouth opening simple and with appendages. Ova yellow to brown, 50 to 54 millimeters long by 23 millimeters broad; unsegmented in fresh fæces.

Habitat.—Cæcum and, less frequently, colon and ileum of man, apes, and the lemur.

Development.—Simple, without intermediate host. Embryo develops in water or moist earth in from 3 to 6 months or longer and will remain alive in its shell for several years unless ingested by its final host when it hatches and reaches sexual maturity in the cæcum after about 16 days.

The resistance to the action of physical and chemical agents shown by both the parent and eggs is remarkable. The parasite is the most difficult of any to destroy in the intestine. The ordinary anthelmintics as a rule have little or no effect upon it. The eggs may be frozen or completely dried without doing them permanent injury.

MODES OF TRANSMISSION.—*Direct:* Inasmuch as an intermediate host is not necessary for the propagation of this parasite, and inasmuch as contact with fæcal discharges is necessary in order to receive the eggs into the gastro-intestinal canal, infection proves a closer personal contact with filth than is true of many other parasitic infections. However, because of the slow development of the eggs under outside influences, immediate transmission from person to person or auto-reinfection can not occur.

Water when contaminated with fæcal discharges, directly or indirectly, may become a transmitter of infection, but because of the rapidity with which the eggs are sedimented in water, it would seem as if this were a much less important medium of transmission than it is generally considered to be.

Food, particularly uncooked vegetables, and to a less extent, fruits, are undoubtedly a means of transmission in a considerable number of instances. On two occasions during our study of the washing from fresh vegetables for the presence of amœbæ, ova of *Trichuris* were found in the sedimented material. The danger from fresh vegetables is great in those countries where human fæces are used as fertilizer for the vegetable gardens. Although this procedure is a violation of the law, it is certainly practiced to a considerable extent by Chinese gardeners in the Philippines, as it is in several other oriental countries.

Insects, such as flies, water bugs, roaches, etc., may be factors of some importance as transmitters of the infection by mechanically carrying it from infected fæces to food and water supplies.

Soil, in localities where methods of sewage disposal are primitive, surely becomes infected and because of the great viability of the eggs in earth, such places become a menace in many obvious ways. So-called clay eaters would be especially liable to infection.

Air, clothing, dust and other substances may be considered as possible factors in the spread of the infection in a mechanical way.

Animals.—Several authors have called attention to the possible inflence of animals in the transmission of this infection. When it is remembered that some domestic animals used as pets may harbor this parasite, and that from their habits several of them are likely to have the eggs in their hair, it would seem that animals might be expected to be occasional transmitters of the infection, particularly among children.

PATHOGENICITY.—The largely accepted commensalism of this parasite is not in accord with the majority of the carefully reported observations (see literature review), nor is it borne out by study of our cases. Belief in the harmless character of *Trichuris* is based largely upon two observations: first, the great, general prevalence of the parasite without symptoms, and second, no satisfactory explanation of the nature of its pathogenic action has been offered.

If we examine the first of these in comparison with some other parasitic infections we find it to be a difference in *degree only* and not a peculiar condition. For example, *Uncinaria* are accepted as pathogenic parasites and yet in our service more than 90 per cent of individuals harboring the worm show no symptoms whatever of the infection. The first symptoms of infection with amœbæ may be those of peritonitis from a perforating ulcer.

Strongyloides stercoralis is now generally accepted as a pathogenic parasite, and yet in the vast majority of instances no symptoms are produced by its presence, and similar statements may be made regarding *Balantidium coli, Dibothriocephalus latus* and a number of other parasites usually accepted as pathogenic.

The percentage of cases infected with *Trichuris* without symptoms probably is greater than for any of the above-named parasites, but infections do occur which produce symptoms and the degree of difference does not appear to be great enough to justify it as an argument for the commensalism of *Trichuris.*

As to the second of the two views, that no satisfactory explanation of the nature of the infection has been made, we may at least in part answer that here the difference from some of the other parasites is also one of degree. No satisfactory explanation of the exact manner of the production or character of the lesions, produced by the majority of the intestinal parasites of man, has been offered.

The pathogenic character of *Trichuris* has been explained by considering it to be a blood sucker; by believing it to produce a hæmolytic substance such as is also acredited to hook-worms; by the formation by it of a toxin; by mechanical action and by its producing perforations which open a way for the entrance of bacteria. None of these explanations is supported by sufficient data to justify its acceptance. The majority of the repeated statements that the parasite is a blood sucker are credited to Askanazy. What Askanazy actually said was that he had isolated "an iron containing pigment from the epithelial cells of the intestine of the parasite." So far as we know, neither blood nor other positive evidence of blood absorption has been found in *Trichuris.*

These parasites do attach themselves to the intestinal wall during the life of the host by transfixation and direct penetration by the head end, and that these locations may show bright, hyperæmic spots and become eroded or even ulcerated, is proved beyond doubt. However, the lesions formed by this action are not as a rule sufficient to explain the symptoms, unless we accept some peculiar hæmolytic or other toxic action of the parasite. It is certain that the mechanical loss of blood from these infections is not sufficient to account for the symptoms and a definite toxic action has not been proved. The nervous symptoms and some of the gastro-intestinal ones might be explained from the mechanical action of the parasites by an hypothesis similar to that of Mayo's embryologic formation used for the explanation of similar symptoms in certain cases of chronic appendicitis and gall bladder diseases. However, this is only a hypothesis and does not account for the severe anæmia, which after all is the important manifestation. The nature of the action of these parasites in producing disease has not been satisfactorily explained, but this should not be accepted as proof of their commensalism.

PATHOLOGY.—The general pathologic changes in fatal cases of trichocephaliasis are severe, secondary anæmia. The special conditions are the presence of the worms and certain changes at their points of attachment to the mucous membrane of the bowel or appendix. Several changes have been described by different authors, which in the main are hyperæmia of the mucosa with hæmorrhagic points; erosions and superficial ulceration of the mucous membrane, surrounded by areas of cell infiltration; and in some instances deep ulceration or other inflammatory reactions extending to the muscular coat of the bowel. Several observers have shown that the worms are attached to the mucous membrane during the life of the patient. They attach themselves by transfixing a fold of mucous membrane, by penetrating the glandular follicles, and by direct perforation, the head being embedded in the deeper layers of the bowel wall. After the death of the patient, the worms detach themselves and at autopsy are usually found free in the bowel. Several authors have demonstrated this direct attachment to the intestine. Corroborative evidence is furnished by the fact that they do not appear in the discharges even after violent purgation. The worms were not passed in a number of cases of successful treatment, when the disappearance of eggs from the fæces showed that they had been destroyed. In these instances we can only assume that the parasites have been killed and remain attached to the mucous membrane of the intestine after death.

INCIDENCE.—This is one of the most frequent of all parasitic infections of man and Garrison has shown it to be the most prevalent in the Philippine Islands.

Some of the statistics in percentages are as follows:

French & Boycott (1905), London 7.8; (1887), Erlangen, 11.1; (1887), Erlangen (Insane), 100. Leukart (1887), Dresden, 2.5; (1887), Kiel, 32.2; (1879), Dublin, 90. Cobbold (1879), Greenwich, 69; (1877), Paris, 50. Davaine (1877), Naples, 100. Blanchard (1889), Bale, 23.6. Garrison, Ranson, and Stevenson

(1903), United States (Insane), 16.8. Heisig (1893), Germany, 45.21. Gubareff (1896), Russia, 43. Boycott (1904), England (Cornwall), 38.78. Grechaninoff (1890), St. Petersburg, 26.41. Sievers (1887), Kiel, 19.81. Roth (1877–1880), Bale, 26.67. Gribbohm (1872–1877), Kiel, 32.20. Heller (1872–1875), Kiel, 30.60. Müller (1862–1873), Erlangen, 11.11. Müller (1852–1862), Dresden, 2.57. Stiles and Garrison (1906), United States (Insane), 7.72. Cima (1893 and 1896), Italy, 37.27. Anæmia Commission (1904), Porto Rico, 7.27. Daniels (1901), Africa, 2.79. Fearnside (1900), India, 6.95. Dobson (1893), India, 4.40. Garrison (1908), Philippine Islands, 59.

Some of the figures included in the series are from examinations of only a few cases or were compiled under conditions which prevented the findings being properly considered as an index of the prevalence of the infection in the general population of the community in which the examinations were made.

Garrison's large and carefully worked out statistics show the highest percentage of infection among the general population as yet reported for any country.

The *incubation* period in this disease would be the time for development of the ingested embryo to maturity which, to judge from the few available data, is more than four weeks.

SYMPTOMS.—We recognize for convenience in discussion *mild* and *severe* intestinal trichocephaliasis and trichocephaliasis of the *appendix*. In general the symptoms may be said to depend upon the severity and location of the infection. In *mild* cases of intestinal infection there are no noticeable symptoms and the patient may harbor the parasites in considerable numbers for a long time without inconvenience. In *severe* infections the symptom complex is largely that of a severe secondary anæmia, with pronounced nervous symptoms and some gastro-intestinal disturbance. The early symptoms vary somewhat in different cases. Usually there is weakness, shortness of breath, nausea, vomiting, diarrhœa, cramps in the muscles, nervousness, insomnia, and a gradually developing anæmia. The condition is as a rule progressive, with accentuation of the principal symptoms as the disease advances.

Circulatory system.—Weakness, with shortness of breath and palpitation of the heart are often early symptoms and become more marked as the disease progresses. Evidences of anæmia, such as pallor of the mucous membrane, œdema, and hæmic murmur of the heart have been noted in several cases. As a rule the spleen is not enlarged and in fact, it may be smaller than normal. The blood picture is largely that of secondary anæmia. There is a decrease in the number of red cells, with poikilocytosis, but nucleated cells are not as a rule present. The number of the leucocytes remains approximately normal and the differential count usually shows a slight relative increase in mononuclears. Slight eosinophilia has been noted, but most observers agree that the eosin cells are not increased and in our cases eosinophilia was absent. No eosin cells were ever found in our Case No. 1. The hæmoglobin is reduced and may be very low before death.

The symptoms in the *respiratory system* may consist of some dyspnœa and cough, when severe anæmia is present.

The *alimentary system* as a rule suffers rather severely. Nausea and vomiting are frequent and annoying symptoms, anorexia and dyspeptic symptoms are also often encountered, although the appetite may remain good throughout the course of the disease. The mucous membranes are pale, the tongue often large and flabby and in two of our cases it showed a dark band down the center, similar to that which has been described for uncinariasis. There may, or may not, be tenderness and pain in the gastric region and in the two cases where it has been recorded, examination of the stomach contents showed nothing abnormal. More or less abdominal discomfort or even pain has been a feature of the majority of cases which have been described and diarrhœa has been present in most of them. The character and number of the intestinal discharges varies, ranging from only one or two stiff, pasty stools in twenty-four hours, to the severest form of diarrhœa, even with bloody discharges. Again, the bowel movements may appear normal for considerable periods of time. Whatever the number and character of the bowel movements, tenesmus and other symptoms indicating involvement of the lower bowel are rare. Stool examinations demonstrate the eggs of the *Trichuris;* at times but few, and again large numbers may be seen in a single field of the microscope. The *urinary, reproductive,* and *locomotor systems* do not, as a rule, show any characteristic symptoms. Muscular cramps, particularly in the calves of the legs, have been repeatedly observed. The urine is usually normal. The *cutaneous system* shows the changes due to anæmia. There may be more or less œdema of dependent parts and even anasarca may develop. The superficial lymphatics are not enlarged.

The *nervous* symptoms are usually quite noticeable and consist of mental and nervous depression which may be melancholic in character; there is often great restlessness, headache, and sometimes insomnia. Objectively nothing of importance is found.

Among the symptoms of the *special senses* aphasia is frequent and it is difficult to explain. Tinnitus aurium and even partial deafness have also been noted by several observers.

Appendiceal trichocephaliasis has not heretofore received much attention. Metchinkoff urged its importance and reported a convincing case in detail. Very little is given about the clinical findings, but *a priori* there is no reason to assume that they would be materially different from appendicitis of other etiology.

Trichocephaliasis of animals has been observed by several authors.

Analysis of symptoms.—As pointed out by Becker, the symptoms in the majority of cases of this disease fall into three groups:

(1) Those of the blood, (2) nervous and (3) gastro-intestinal symptoms.

These are present to a greater or less extent in all cases of severe infection. The blood changes and the anæmia point positively to what we recognize as a secondary type of the latter. The absence of eosinophilia is quite generally recognized and is to be noted. French and Boycott paid particular attention to this condition and failed to find eosinophilia in 26 cases which they examined. In ours, eosinophilipænia was the rule, and in Case No. 1 no eosinophile cells were ever found after repeated blood examinations.

The nervous symptoms are difficult to explain, particularly the mental and nervous depression and the aphasia which has been so frequently noted, and it is probable that the nausea and vomiting are to a considerable extent of nervous origin.

Even the intestinal symptoms are difficult to explain as a result of the pathologic findings, certainly they are not to be considered as being due to the direct loss of blood caused by the mechanical action of the worms. Marsasca and others believe that the latter secrete a special toxin, and although the entire clinical picture supports such a view, it has not been demonstrated. Bacteria and other secondary invaders entering through the injured mucosa probably account for some of the symptoms and explain those cases having septicæmia. However, the manner of the production of the symptoms remains unexplained.

DIAGNOSIS.—While the clinical picture in some of these cases is quite suggestive, diagnosis can only be determined by finding the eggs of the parasite in the stools. Not every patient having eggs in the stools will show symptoms of the infection, and for clinical purposes only a combination of some of the clinical phenomena and the presence of eggs should be considered as a diagnosis from a practical therapeutic standpoint. The differentiation from most of the other recognized types of anæmia is readily made by the blood picture. Severe infections are only differentiated clinically from similar cases of uncinariasis by stool examinations and by the greater prevalence of eosinophilia in the hook-worm infections.

PROGNOSIS.—Certain light infections do not appear to do recognizable harm, even when the parasites remain for a long time in the bowel. The prognosis in severe infections is grave, largely because of the difficulty with which the parasites are destroyed. Barth, Pascal, Sandler, Moosbrugger and others have reported fatal cases. The disease may continue for a long time, and, on the other hand, as in our Case No. 1, the course may be fairly acute and its duration from the development of clinical symptoms short.

PROPHYLAXIS.—The prevention of this disease consists in personal hygiene and in public health measures. Because of the simple life cycle of the parasite and the long viability of the eggs under outside influences, personal hygiene, by avoiding the introduction of unsterilized substances into the mouth, makes protection fairly safe even in infected zones.

The hygienic side of the problem requires a safe and practical method for the disposal of fæces. This is very important, not only because of the presence of whip-worms, but of others as well. This subject has been covered by Garrison (30).

TREATMENT.—Whip-worms are exceedingly difficult to destroy in the intestine. In this respect out experiences have been in conformity with the general literature of the subject. However, several authors have had more or less success with various anthelmintics, *and in most cases where it has been possible to destroy the worms, rapid and complete recovery of the patient has followed.* Enemas of solutions of benzine have been the most successful in the hands of several observers, while others have reported success by the use of calomel, thymol, naphthol, santonin, or garlic. We have used thymol, the eucaliptus oil, chloroform, and the castor oil mixtures employed for uncinariasis, but without very much success. The benzine treatment has only just come to our notice, but to judge from the reports in the literature it deserves a more extended trial. Schiller (quoted by Sandler (74)) used thymol by mouth and benzine solutions as enemas and secured 2,000 worms from one case. This is remarkable because of the fact that the worms were passed. The killed worms in the experience of most authors do not pass from the bowel and their destruction is only made evident by the disappearance of the eggs from the stools. Other treatment of the disease consists in general hygienic measures with attempts to improve the nutrition of the patient.

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EDITORIAL.

NEOPLASMS AMONG THE FILIPINOS.

It has been variously stated by different writers that new growths and more especially malignant tumors, are not only less common than in temperate climates, but even rare in many tropical countries. There was a more or less well-defined idea prevalent among the profession in Manila that in the native inhabitants of the Philippines neoplasms are uncommon, but no complete records were available bearing on the point.

Malignant disease as a cause of death occurred twice among the first series of 100 necropsies at the Philippine Medical School; 2 cases of carcinoma of the greater curvature of the stomach, and 1 of the cheek and antrum.

Dudley,[1] writing on the prevalence of cancer in the Philippines after an experience of ten years spent in the various islands, believes that cancer exists in the Philippines to a greater extent than in the United States, and that the statistics available on malignant and nonmalignant growths are very incomplete.

The following figures illustrating the frequency of neoplasms in Dr. McDill's surgical clinic at the St. Paul's Hospital may be taken as fairly typical, as the clinic draws on all classes of free patients, the material coming not only from the city of Manila, but from the surrounding and often distant provinces.

The record of cases coming to operation from September 5, 1907, up to December 19, 1908, shows a total of 377. Sixty-five of these cases, or 17.4 per cent, were operations for new growths, 37 benign and 28 malignant.

Of the benign neoplasms, cystic ovarian disease leads in frequency, there being 16 cases, of which 4 were double. Of uterine fibroids there were 7 cases, the most frequent being the sub-serous variety. There were 5 cases of fibromata of the skin and 2 each of osteomata of the head and intracanalicular myxomata of the breast. There was but one case of adenoma of the breast; one dentigerous cyst of the lower jaw; one cyst of the neck (thyroglossal duct); one cyst of the anterior wall of the vagina, and one epulis.

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[1] The Prevalence of Cancer in the Philippine Islands, *Journ. Amer. Med. Ass.* (1908), **50**, 1663 to 1665.

Of the 28 cases of malignant growths there were 13 sarcomata, 12 carcinomata, and 3 of Hodgkin's disease. The sarcomata involved the scalp, testicle, femur, and dorsum of the foot twice; the forearm, eye, parotid, tibia, and skin once.

There were 6 cases of carcinoma of the stomach. The breast was carcinomatous in 2 cases, the pancreas, uterus, liver, and skin one each. The 3 cases of Hodgkin's disease all showed involvement of the supraclavicular and axillary glands.

PHILIP K. GILMAN.

REVIEW.

A Text-Book of the Principles of Animal Histology. By Ulric Dahlgren, M. S. and William A. Kepner, A. B. Cloth. Pp. xiii+515. Price, $3.75 net. New York: The Macmillan Company, 1908.

This work of more than 500 pages, containing nearly 500 illustrations of which about 300 are original, has had such a flattering reception and has been so favorably reviewed that it is unnecessary further to discuss its value. The authors state that the book "is intended to be a work that teaches general principles and teaches histology as a pure science and for its own sake. It is believed that it will serve as a broad foundation for future studies of morphology and embryology as well as for the medical studies." This object is well fulfilled. Rich fields heretofore untouched by any text-book, such as the tissues that produce electricity, light, gases, etc., are opened, offering the results of original research work on these subjects.

The illustrations are not only largely original, but they explain the text by their clearness and detail. Many of them are diagrammatic, thus furnishing an ideal method of instruction without sacrificing reality. In this way the structure of protoplasm is made plain, chromatin changes become distinct, the amplification of body surface is illustrated, the arrangements of muscles' cells is explained, the relation of absorptive surface is indicated, and many other obscure points are made clear. A bit of muscle fiber shows relaxation in the segment at one end and successive stages of contraction in all the other segments, and this is only one of many unusual illustrations.

The comprehensive character of the work is made clear by the following list of tissues, to each of which a chapter is devoted:

Epithelium.
Supporting and connecting tissues.
Tissues of motion.
Electric tissues.
Tissues of light production.
Tissues of heat production.
Circulatory tissues.
Nerve tissues.
Pigment tissues.
Alimentary tissues.
Ductless glands.
Tissues of respiration.
Gas-secreting tissues.
Excretory tissues.
Protective tissues.
Tissues of reproduction.
Nidamental and erectile tissues.
Nourishing membranes.

Improvement in style and in grammatical structure are to be desired and will doubtless be found in future editions of the work, of which it is to be hoped there will be many. If references are given they should be in greater number and form a complete bibliography. However, such a wide range of subjects is covered that an undertaking of this kind is scarcely feasible.

The book is not altogether suitable for beginners, but it is the best that I have seen and I most heartily recommend it to students preparing for medical work.

R. B. B.

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[NOTE.—The heavy-faced type is used in this index only in cases where the species is new, that is, pertaining to this year.]

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